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(71) Applicant: **MERZ PHARMA GMBH & CO. KGAA**
[DE/DE]; Eckenheimer Landstrasse 100, 60318 Frankfurt
am Main (DE).

(72) Inventor: **SCHLEMM, Karsten**; Hornbostelgasse 18,
1060 Wien (DE).

(74) Agent: **RICKER, Mathias**; Wallinger Ricker Schlotter
Tostmann, Patent- und Rechtsanwälte, Partnerschaft mbB,
Zweibrückenstrasse 5-7, 80331 München (DE).

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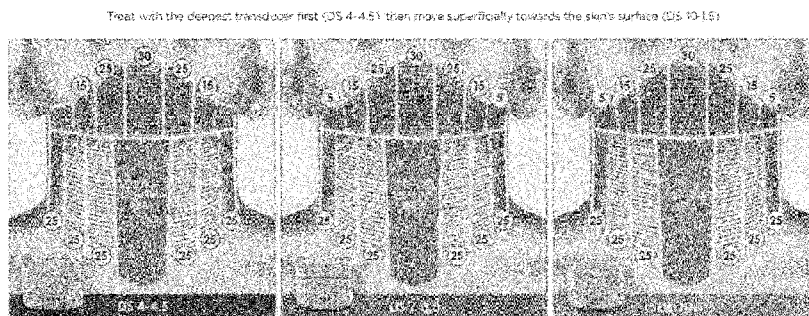
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Figure 68:



(57) Abstract: This invention relates to improvements to ultrasound-based therapy of tissue exhibiting a loss of tightness, in particular photoaged tissue, in particular in combination with a certain clostridial neurotoxin pre-treatment.

IMPROVEMENTS TO ULTRASOUND-BASED THERAPY OF PHOTOAGED TISSUE

FIELD OF THE INVENTION

[001] This invention relates to improvements to ultrasound-based therapy of tissue exhibiting a loss of tightness, in particular photoaged tissue, in particular in combination with a certain clostridial neurotoxin pre-treatment.

BACKGROUND OF THE INVENTION

[002] The treatment of medical and non-medical, including cosmetic, conditions characterized by, caused by, or associated with, tissue exhibiting a loss of tightness, in particular skin, has become more and more important. Such conditions include wrinkles, scars, and photoaged skin.

[003] Photoaging of human skin is a complex response due to inflammation, oxidative injury, cellular and extracellular changes induced by decades of sunlight exposure. UV light is thought to be mainly responsible for the photoaging process, in which both epidermal and dermal skin layers are affected. Epidermal photoaging includes pigmentary lesions called ephelides (freckles) and solar lentigines (larger pigmented spots), plus pre-cancerous clonal lesions of keratinocytes called actinic keratoses. Thermal destruction of part or all of the epidermis, the outermost cellular layer of skin about 0.1 mm thick, is an effective treatment for epidermal photoaging. For example, lasers that vaporize epidermis are highly effective in a treatment called laser resurfacing. However laser resurfacing creates a significant skin wound with risk of infection, and prolonged healing. Dermal changes of photoaging include solar elastosis (an accumulation of abnormally-formed elastin fibers in the upper reticular layer of the dermis), laxity, loss of elasticity, fine and coarse wrinkles. Laser resurfacing to a depth below the dermo-epidermal junction can be highly effective for improving dermal photoaging, through a process of stimulated wound healing. Deep

chemical peels, dermabrasion and other methods of destruction of epidermis and/or dermis are also effective, and also produce a significant open skin wound with risk of infection and delayed healing.

[004] In the past years, an alternative method has been developed for the treatment of tissue exhibiting a loss of tightness, in particular the treatment of photoaged tissue, which is based on the use of ultrasound. This method has recently been approved in the US (Ultherapy®). In particular, Ultherapy® uses focused, unfocused, and/or defocused ultrasound for treatment of epidermal, superficial dermal, dermal, mid-dermal, and/or deep dermal components of photoaged tissue by adjusting the strength, depth, and/or type of focusing, energy levels and timing cadence. For example, focused ultrasound can be used to create precise arrays of microscopic thermal damage much deeper into the skin or even into subcutaneous structures. Detection of changes in the reflection of ultrasound can be used for feedback control to detect a desired effect on the tissue and used to control the exposure intensity, time, and/or position. More details are provided in US 8,641,622. Ultherapy® finds widespread applications in the remodelling of the skin surface by modifying the dermal and/or muscle tissue associated with the affected skin surface and has in particular been approved in the US for use on the face, neck, and décolletage.

[005] Despite the progress that has been made in the past in the treatment of tissue exhibiting a loss of tightness, in particular the treatment of photoaged tissue, by using Ultherapy®, there is still a strong demand to further improve the therapeutic options available to the practitioner in the art, in particular in the case of skin areas situated in areas of the body associated with increased muscle tonus. To date, such aspects have not been addressed satisfactorily.

OBJECTS OF THE INVENTION

[006] It was an object of the invention to provide improvements to ultrasound-based therapy of tissue exhibiting a loss of tightness; in particular photoaged tissue, in

particular in skin areas situated in areas of the body associated with increased muscle tonus.

SUMMARY OF THE INVENTION

[007] The present invention is based on the surprising finding that ultrasound-based therapy of medical and non-medical, including cosmetic, conditions characterized by, caused by, or associated with, tissue exhibiting a loss of tightness, in particular of photoaged tissue, in skin areas situated in areas of the body associated with high muscle tension particularly benefits from a preceding treatment of the corresponding muscles with a muscle relaxant, in particular wherein said muscle relaxant is a clostridial neurotoxin.

[008] Thus, the present invention relates in a first aspect to a clostridial neurotoxin for use in the treatment of a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, wherein said treatment comprises the steps of (i) applying said clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of the body associated with high muscle tension; and (ii) applying ultrasound, in particular high-frequency ultrasound, to the tissue treated with said clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used that is configured to apply ultrasonic energy to a linear focal zone at a focal depth.

[009] In a second aspect the present invention relates to a method of treating a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, comprising the steps of (i) applying a clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of said tissue associated with high muscle tension; and (ii) applying ultrasound, in particular high-frequency ultrasound, to the tissue treated with said clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used that is configured to apply ultrasonic energy to a linear focal zone at a focal depth.

[0010] Furthermore, the present invention more generically relates in another aspect to a clostridial neurotoxin for use in the treatment of a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, wherein said treatment comprises the step of (i) applying said clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of the body associated with high muscle tension.

[0011] Furthermore, the present invention more generically relates in another aspect to a method of treating a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, comprising the steps of (i) applying a clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of said tissue associated with high muscle tension.

In the process of neocollagenesis the areas, which were treated with ultrasound, are slowly infiltrated with new collagen fibres. In the beginning of this process the fibres are very thin and widely spread. The muscle movements can rupture the fibres or prolong the building of the fibres, which causes prolongation of the neocollagenesis. Therefore it is important, that during the neocollagenesis the surrounding area is as relaxed as possible. The treatment with a clostridial neurotoxin in the surrounding area of the region treated with Ultherapy® can relax the muscle and consequently support the undisturbed building of new collagen fibres and connections. A combination of clostridial neurotoxin before or simultaneous with Ultherapy® is thus very helpful.

FIGURES

[0012] The drawings described herein are for illustration purposes only and are not intended to limit the scope of the present disclosure in any way. Embodiments of the present invention will become more fully understood from the detailed description and the accompanying drawings.

[0013] **Figure 1** is a schematic illustration of an ultrasound system according to various embodiments of the present invention.

[0014] **Figure 2** is a schematic illustration of an ultrasound system coupled to a region of interest according to various embodiments of the present invention.

[0015] **Figure 3** illustrates a schematic cross-sectional side view of a cylindrical transducer in a cosmetic treatment system according to an embodiment. Although a cylinder transducer is illustrated here, the transducer need not be cylindrical. In several embodiments, the transducer has one or more shapes or configurations that cause edge effects, such as variance, spikes or other inconsistencies in the delivery of ultrasound. For example, the transducer may have one or more non-linear (e.g., curved) portions.

[0016] **Figure 4** illustrates a schematic isometric side view of a sectioned cylindrical transducer of Figure 3.

[0017] **Figures. 5A - 5B** illustrate a schematic isometric side view of a cylindrical transducer being moved by a motion mechanism in a cosmetic treatment system, wherein the thermal treatment zone (TTZ) sweeps a treatment area, according to an embodiment.

[0018] **Figure 6** illustrates a schematic exploded isometric view of a cylindrical transduction element in a cosmetic treatment system according to an embodiment.

[0019] **Figure 7** illustrates a schematic isometric view of the cylindrical transduction element of Figure 6 with a motion mechanism in a cosmetic treatment system according to an embodiment.

[0020] **Figure 8** illustrates a schematic isometric view of the cylindrical transduction element with a motion mechanism of Figure 7 in a probe housing of a cosmetic treatment system according to an embodiment.

[0021] **Figure 9** is a schematic partial cut away illustration of a portion of a transducer according to various embodiments of the present invention.

[0022] **Figure 10** is a partial cut away side view of an ultrasound system according to various embodiments of the present invention.

[0023] **Figures 11A-11B** are schematic illustrations and plots illustrating normalized pressure intensity distributions at a depth of 20 mm according to an embodiment of a transducer comprising a cylindrical transduction element.

[0024] **Figures 12A-12B** are schematic illustrations and plots illustrating normalized pressure intensity distributions at a depth of 15 mm according to the embodiment of a transducer comprising a cylindrical transduction element of Figures 11A-11B.

[0025] **Figures 13A-13B** are schematic illustrations and plots illustrating normalized pressure intensity distributions at a depth of 13 mm according to the embodiment of a transducer comprising a cylindrical transduction element of Figures 11A-11B.

[0026] **Figures 14A-14B** are schematic plots illustrating normalized pressure intensity distributions at a depth of 20 mm according to an embodiment of a transducer comprising a cylindrical transduction element.

[0027] **Figures 15A-15B** are schematic plots illustrating normalized pressure intensity distributions at a depth of 15 mm according to the embodiment of a transducer comprising a cylindrical transduction element of Figures 11A-11B.

[0028] **Figures 16A-16B** are schematic plots illustrating normalized pressure intensity distributions at a depth of 13 mm according to the embodiment of a transducer comprising a cylindrical transduction element of Figures 11A-11B.

[0029] **Figure 17** is a plot illustrating temperature in porcine muscle over time at different power levels for an embodiment of a transducer comprising a cylindrical transduction element.

[0030] **Figure 18** is a photograph of porcine muscle after experimental treatment confirming confirmed line and plane heating with an embodiment of a transducer comprising a cylindrical transduction element.

[0031] **Figure 19** is a cross-section cut through the porcine muscle in Figure 18 showing a linear thermal treatment zone.

[0032] **Figure 20** is an orthogonal cross-section cut through the porcine muscle in FIG. 19 showing a planar thermal treatment zone.

[0033] **Figure 21** is a cross-section view of a combined imaging and cylindrical therapy transducer according to an embodiment of the present invention.

[0034] **Figure 22** is a side view of a combined imaging and cylindrical therapy transducer according to Figure 21.

[0035] **Figure 23** is a plot illustrating harmonic pressure across an azimuth of an embodiment of a cylindrical element with an imaging element.

[0036] **Figure 24** is a plot illustrating harmonic pressure across an azimuth of an embodiment of a coated cylindrical element with an imaging element.

[0037] **Figure 25** is a plot illustrating harmonic pressure across an azimuth of an embodiment of a cylindrical element with an imaging element compared to an embodiment of a coated cylindrical element with an imaging element.

[0038] **Figure 26** is a side view of a coated transducer comprising a cylindrical transduction element with one or more coated regions according to an embodiment of the present invention.

[0039] **Figure 27** is a plot illustrating focal gain across the azimuth of two embodiments of cylindrical transduction elements.

[0040] **Figure 28** is a schematic plot illustrating normalized pressure intensity distributions at a depth distal to the focal zone by about 5 mm according to an embodiment of a coated transducer comprising a cylindrical transduction element with one or more coated regions.

[0041] **Figure 29** is a schematic plot illustrating normalized pressure intensity distributions at a focal depth according to the embodiment of the coated transducer of Figure 28.

[0042] **Figure 30** is a schematic plot illustrating normalized pressure intensity distributions at a depth proximal to the focal depth by about 2 mm according to the embodiment of the coated transducer of Figure 28.

[0043] **Figure 31** is a side view of a coated transducer according to an embodiment of the present invention.

[0044] **Figure 32** is a side view of a coated transducer according to an embodiment of the present invention.

[0045] **Figure 33** is a side view of a coated transducer according to an embodiment of the present invention.

[0046] **Figure 34** is a side view of a coated transducer according to an embodiment of the present invention.

[0047] **Figure 35** is a side view of a coated transducer according to an embodiment of the present invention.

[0048] **Figure 36** is a side view of a coated transducer according to an embodiment of the present invention.

[0049] **Figure 37** is a side view of a coated transducer according to an embodiment of the present invention.

[0050] **Figure. 38** is a side view of a coated transducer according to an embodiment of the present invention.

[0051] **Figure 39** illustrates a charts relating time and temperature to attain various theoretical cell kill fractions according to an embodiment of the present invention.

[0052] **Figure 40** illustrates charts relating time and temperature to attain various theoretical cell kill fractions according to an embodiment of the present invention.

[0053] **Figure 41** is a table listing isoeffective dosages to theoretically achieve 1% survival fraction in tissue, listing temperature and time, according to an embodiment of the present invention.

[0054] **Figure 42** is a chart relating time and temperature for isoeffective doses applied for surviving fraction of cells according to an embodiment of the present invention.

[0055] **Figure 43** illustrates simulations of cylindrical transducer output showing linear superposition of multiple pulses according to an embodiment of the present invention.

[0056] **Figure 44** is a top view of an apodized transducer according to an embodiment of the present invention.

[0057] **Figure 45** illustrates acoustic pressure profiles with an apodized transducer according to the embodiment of Figure 44.

[0058] **Figure 46** is a chart illustrating temperature profiles from an embodiment of an in-vivo porcine model treatment dosage study according to an embodiment of the present invention.

[0059] **Figure 47** is a chart for setting for an isoeffective dosage study according to an embodiment of the present invention.

[0060] **Figure 48** illustrates cumulative dose relating time, temperature, and pass count of a treatment study according to an embodiment of the present invention.

[0061] **Figure 49** is a table with target temperatures and time for a treatment study according to an embodiment of the present invention.

[0062] **Figure 50** is a table with various embodiments of transducers treatments settings for an isoeffective thermal dosage treatment study according to an embodiment of the present invention.

[0063] **Figure 51** is an image of a thermally overdosed site with a transducer according to an embodiment of the present invention.

[0064] **Figure 52** is chart relating time and temperature with target goal temperatures according to an embodiment of the present invention.

[0065] **Figure 53** is an isometric side view of a transducer and treatment area according to an embodiment of the present invention.

[0066] **Figure 54** is a chart illustrating velocity and position along an axis according to an embodiment of the present invention.

[0067] **Figure 55** is a chart illustrating velocity and position along an axis according to an embodiment of the present invention.

[0068] **Figure 56** is a chart illustrating amplitude and position along an axis according to an embodiment of the present invention.

[0069] **Figure 57** is a chart illustrating velocity and position along an axis according to an embodiment of the present invention.

[0070] **Figure 58** is a chart illustrating velocity and position along an axis according to an embodiment of the present invention.

[0071] **Figure 59** illustrates a non-overlapping treatment according to an embodiment of the present invention.

[0072] **Figure 60** illustrates a partially overlapping and a partially non-overlapping treatment according to an embodiment of the present invention.

[0073] **Figure 61** illustrates a treatment area according to various embodiments of the present invention.

[0074] **Figure 62** is a chart illustrating intensity and depth according to an embodiment of the present invention.

[0075] **Figure 63** is an isometric side view of a transducer and treatment area with multiple thermal treatment zones according to an embodiment of the present invention.

[0076] **Figure 64** is a schematic side view of a system comprising a plurality of ultrasound elements on a motion mechanism according to an embodiment of the present invention.

[0077] **Figure 65** is a picture showing the areas and lines of treatment for facial tissue with focal depth of 4.5 mm.

[0078] **Figure 66** is a picture showing the areas and lines of treatment for facial tissue with focal depth of 3.0 mm.

[0079] **Figure 67** is a picture showing the areas and lines of the optional treatment for facial tissue with focal depth of 1.5 mm.

[0080] **Figure 68** is a picture showing the areas and lines of treatment for neck tissue.

[0081] **Figure 69** is a picture showing the areas and lines of treatment for chest tissue.

DETAILED DESCRIPTION OF THE INVENTION

[0082] The present invention may be understood more readily by reference to the following detailed description of the invention and the examples included therein.

[0083] Thus, in a first generic aspect, the present invention relates to a clostridial neurotoxin for use in the treatment of a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, wherein said treatment comprises the step of (i) applying said clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of the body associated with high muscle tension.

[0084] In particular embodiments, the treatment is a medical treatment, which is a method for treatment of the human or animal body by surgery or therapy practised on the human or animal body.

[0085] In a second generic aspect the present invention relates to a method of treating a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, comprising the steps of (i) applying a clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of said tissue associated with high muscle tension.

[0086] In particular embodiments, the treatment is a medical treatment, which is a method for treatment of the human or animal body by surgery or therapy practised on the human or animal body.

[0087] In particular other embodiments, the treatment is a non-medical treatment, which is not a method for treatment of the human or animal body by surgery and/or therapy practised on the human or animal body. Such methods in particular include cosmetic treatments.

[0088] The administration of ultrasound towards tissue results in tissue heating, tissue pre-heating, a face lift, a brow lift, a chin lift, an eye treatment, a wrinkle reduction, treatment of décolletage, a scar reduction, a burn treatment, a tattoo removal, a vein removal, a vein reduction, a treatment on a sweat gland, a treatment of hyperhidrosis, a fat or adipose and/or cellulite reduction, a sun spot removal, an acne treatment, a pimple reduction.

[0089] In another embodiment the system, device and/or method may be applied in the genital area (e.g., vaginal rejuvenation and/or vaginal tightening, such as for tightening the supportive tissue of the vagina).

[0090] In the context of the present invention, the term “photoaged tissue” refers to all skin layers (including SMAS), which have lost their firmness and tightness in an age-, light- and/or tension-dependent manner.

[0091] In the context of the present invention, the term “skin areas situated in areas of the body associated with high muscle tension” refers to all skin areas, which are influenced by muscles like mimic muscles, body muscles, gland muscles or other muscles.

[0092] In the context of the present invention tissue below or at a skin surface such as epidermis, dermis, platysma, lymph node, nerve, fascia, muscle, fat, and/or superficial muscular aponeurotic system (“SMAS”), are treated non-invasively with ultrasound energy.

[0093] Target tissue may be, but is not limited to, any of skin, eyelids, eye lash, eye brow, caruncula lacrimalis, crow's feet, wrinkles, eye, nose, mouth, tongue, teeth, gums, ears, brain, chest, back, buttocks, legs, arms, hands, arm pits, heart, lungs, ribs, abdomen, stomach, liver, kidneys, uterus, breast, vagina, penis, prostate, testicles, glands, thyroid glands, internal organs, hair, muscle, bone, ligaments, cartilage, fat, fat lobuli, adipose tissue, cellulite, subcutaneous tissue, implanted tissue, an implanted organ, lymphoid, a tumor, a cyst, an abscess, or a portion of a nerve, or any combination thereof.

[0094] In the context of the present invention, the term "clostridial neurotoxin" refers to (i) neurotoxins produced by bacteria of the genus *Clostridium*, (ii) the neurotoxic component of such neurotoxins, and/or (iii) to functionally active variants of such neurotoxins and/or neurotoxic components.

[0095] *Clostridium* is a genus of anaerobe gram-positive bacteria, belonging to the Firmicutes. *Clostridium* consists of around 100 species that include common free-living bacteria as well as important pathogens, such as *Clostridium botulinum* and *Clostridium tetani*. Both species produce neurotoxins, botulinum toxin and tetanus toxin, respectively. These neurotoxins are potent inhibitors of calcium-dependent neurotransmitter secretion of neuronal cells and are among the strongest toxins known to man. The lethal dose in humans lies between 0.1 ng and 1 ng per kilogram of body weight.

[0096] Oral ingestion of botulinum toxin via contaminated food or generation of botulinum toxin in wounds can cause botulism, which is characterised by paralysis of various muscles. Paralysis of the breathing muscles can cause death of the affected individual.

[0097] Although both botulinum neurotoxin (BoNT) and tetanus neurotoxin (TxNT) function via a similar initial physiological mechanism of action, inhibiting neurotransmitter release from the axon of the affected neuron into the synapse, they differ in their clinical response. While the botulinum toxin acts at the neuromuscular junction and other cholinergic synapses in the peripheral nervous system, inhibiting

the release of the neurotransmitter acetylcholine and thereby causing flaccid paralysis, the tetanus toxin acts mainly in the central nervous system, preventing the release of the inhibitory neurotransmitters GABA (gamma-aminobutyric acid) and glycine by degrading the protein synaptobrevin. The consequent overactivity in the muscles results in generalized contractions of the agonist and antagonist musculature, termed a tetanic spasm (rigid paralysis).

[0098] While the tetanus neurotoxin exists in one immunologically distinct type, the botulinum neurotoxins are known to occur in eight different immunogenic types, termed BoNT/A through BoNT/H. Most *Clostridium botulinum* strains produce one type of neurotoxin, but strains producing multiple toxins have also been described.

[0099] Botulinum and tetanus neurotoxins have highly homologous amino acid sequences and show a similar domain structure. Their biologically active form comprises two peptide chains, a light chain of about 50 kDa and a heavy chain of about 100 kDa, linked by a disulfide bond. A linker or loop region, whose length varies among different clostridial toxins, is located between the two cysteine residues forming the disulfide bond. This loop region is proteolytically cleaved by an unknown clostridial endoprotease to obtain the biologically active toxin.

[00100] The molecular mechanism of intoxication by TxNT and BoNT appears to be similar as well: entry into the target neuron is mediated by binding of the C-terminal part of the heavy chain to a specific cell surface receptor; the toxin is then taken up by receptor-mediated endocytosis. The low pH in the so formed endosome then triggers a conformational change in the clostridial toxin which allows it to embed itself in the endosomal membrane and to translocate through the endosomal membrane into the cytoplasm, where the disulfide bond joining the heavy and the light chain is reduced. The light chain can then selectively cleave so called SNARE-proteins, which are essential for different steps of neurotransmitter release into the synaptic cleft, e.g. recognition, docking and fusion of neurotransmitter-containing vesicles with the plasma membrane. TxNT, BoNT/B, BoNT/D, BoNT/F, and BoNT/G cause proteolytic cleavage of synaptobrevin or VAMP (vesicle-associated membrane protein), BoNT/A and BoNT/E cleave the plasma membrane-associated protein

SNAP-25, and BoNT/C cleaves the integral plasma membrane protein syntaxin and SNAP-25.

[00101] In *Clostridium botulinum*, the botulinum toxin is formed as a protein complex comprising the neurotoxic component and non-toxic proteins. The accessory proteins embed the neurotoxic component thereby protecting it from degradation by digestive enzymes in the gastrointestinal tract. Thus, botulinum neurotoxins of most serotypes are orally toxic. Complexes with, for example, 450 kDa or with 900 kDa are obtainable from cultures of *Clostridium botulinum*.

[00102] In recent years, botulinum neurotoxins have been used as therapeutic agents, for example in the treatment of dystonias and spasms, and have additionally been used in cosmetic applications, such as the treatment of fine wrinkles. Preparations comprising botulinum toxin complexes are commercially available, e.g. from Ipsen Ltd (Dysport®) or Allergan Inc. (Botox®). A high purity neurotoxic component, free of any complexing proteins, is for example available from Merz Pharmaceuticals GmbH, Frankfurt (Xeomin®). The sequences of the neurotoxic components of the clostridial neurotoxins BoNT/A through BoNT/G and of TxNT are shown in Table 1.

[00103] Clostridial neurotoxins are usually injected into the affected muscle tissue, bringing the agent close to the neuromuscular end plate, i.e. close to the cellular receptor mediating its uptake into the nerve cell controlling said affected muscle. Various degrees of neurotoxin spread have been observed. The neurotoxin spread is thought to depend on the injected amount and the particular neurotoxin preparation. It can result in adverse side effects such as paralysis in nearby muscle tissue, which can largely be avoided by reducing the injected doses to the therapeutically relevant level. Overdosing can also trigger the immune system to generate neutralizing antibodies that inactivate the neurotoxin preventing it from relieving the involuntary muscle activity. Immunologic tolerance to botulinum toxin has been shown to correlate with cumulative doses.

[00104] As mentioned above, the term "clostridial neurotoxin" further includes functionally active variants of clostridial neurotoxins and/or of the neurotoxic components of clostridial neurotoxins. In the context of the present invention, the term "functionally active variant" refers to a neurotoxin, in particular a recombinant neurotoxin, that differs in the amino acid sequence and/or the nucleic acid sequence encoding the amino acid sequence from a parental clostridial neurotoxin or neurotoxic component of a parental clostridial neurotoxin, e.g. from one of the neurotoxic components of the clostridial neurotoxins BoNT/A through BoNT/G and of TxNT obtainable from the single-chain precursor proteins as shown in Table 1 (SEQ ID Nos: 1 to 8), but is still functionally active. In the context of the present invention, the term "functionally active" refers to the property of such recombinant clostridial neurotoxin variant to (i) achieve muscle paralysis to at least 50%, particularly to at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, and most particularly at least 90% of the muscle paralysis achieved with the same amount of the parental clostridial neurotoxin or neurotoxic component of the parental clostridial neurotoxin, and to (ii) achieve muscle paralysis for a duration of time that is at maximum 50% shorter or longer, particularly at maximum 40%, 30%, 25%, 20%, 15% or 10% shorter or longer than the duration of paralysis achieved with the same amount of the parental clostridial neurotoxin or neurotoxic component of the parental clostridial neurotoxin (i.e. which shows between 50% and 150% of the duration of paralysis, particularly between 60% and 140%, 70% and 130%, 75% and 125%, 80% and 120%, 85% and 115%, or 90% and 110% of the duration of paralysis achieved with the same amount of the parental clostridial neurotoxin or neurotoxic component of the parental clostridial neurotoxin).

[00105] Functionally active variants of clostridial neurotoxins with biological activity within the context of the present invention comprise at least one HC-domain of the neurotoxic component of a clostridial toxin or a functionally active fragment thereof and at least one LC-domain of the neurotoxic component of a clostridial toxin or a functionally active fragment thereof.

[00106] A "functionally active fragment of a clostridial HC domain", as used herein, refers to a fragment which is still capable of binding to the HC domain

receptor of the native HC domain, from which it is derived. Moreover, said fragment is also a fragment capable of translocating an LC domain attached to it.

[00107] A “functionally active fragment of the LC domain”, as used herein, refers to a fragment of the LC domain which (still) exhibits the proteolytic activity preferably of the wild-type LC, i.e. which is capable of cleaving a polypeptide of the SNARE complex such as e.g. syntaxin, SNAP-25 or synaptobrevin. Accordingly, biological activity may be tested e.g. by a SNAP-25 protease assay, LD₅₀-Assay, HDA-Assay, a cell-based assay as it is disclosed for example in WO2009/114748, WO 2013/049508 or WO 2014/207109, and the like. Therefore, any LC-domain, which shows proteolytic activity of more than 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and up to 100% of the corresponding wild-type LC-domain in a SNAP-25 assay is considered “biological active” or “to exhibit proteolytic activity” within the scope of this invention.

[00108] On the protein level, a functionally active variant will thus maintain key features of the corresponding parental clostridial neurotoxin, including key residues for the endopeptidase activity in the light chain, and key residues for the attachment to the neurotoxin receptors or for translocation through the endosomal membrane in the heavy chain, but may contain one or more mutations comprising a deletion of one or more amino acids of the corresponding clostridial neurotoxin, an addition of one or more amino acids of the corresponding clostridial neurotoxin, and/or a substitution of one or more amino acids of the corresponding clostridial neurotoxin. Particularly, said deleted, added and/or substituted amino acids are consecutive amino acids. According to the teaching of the present invention, any number of amino acids may be added, deleted, and/or substituted, as long as the variant remains functionally active as defined above. For example, 1, 2, 3, 4, 5, up to 10, up to 15, up to 25, up to 50, up to 100, up to 200, up to 400, up to 500 amino acids or even more amino acids of a parental clostridial neurotoxin may be added, deleted, and/or substituted. This neurotoxin variant may contain an N-terminal, C-terminal, and/or one or more internal deletion(s).

[00109] In another embodiment, the functionally active variant of a clostridial neurotoxin additionally comprises a signal peptide. Usually, said signal peptide will be located at the N-terminus of the neurotoxin. Many such signal peptides are known in the art and are comprised by the present invention. In particular, the signal peptide results in transport of the neurotoxin across a biological membrane, such as the membrane of the endoplasmic reticulum, the Golgi membrane or the plasma membrane of a eukaryotic or prokaryotic cell. It has been found that signal peptides, when attached to the neurotoxin, will mediate secretion of the neurotoxin into the supernatant of the cells. In certain embodiments, the signal peptide will be cleaved off in the course of, or subsequent to, secretion, so that the secreted protein lacks the N-terminal signal peptide, is composed of separate light and heavy chains, which are covalently linked by disulfide bridges, and is proteolytically active.

[00110] In particular embodiments, the functionally active variant has in its clostridium neurotoxin part a sequence identity of at least 40%, at least 50%, at least 60%, at least 70% or most particularly at least 80%, and a sequence homology of at least 60%, at least 70%, at least 80%, at least 90%, or most particularly at least 95% to the corresponding part of a parental clostridial neurotoxin. Methods and algorithms for determining sequence identity and/or homology, including the comparison of variants having deletions, additions, and/or substitutions relative to a parental sequence, are well known to the practitioner of ordinary skill in the art. On the DNA level, the nucleic acid sequences encoding the functional homologue and the parental clostridial neurotoxin may differ to a larger extent due to the degeneracy of the genetic code. It is known that the usage of codons is different between prokaryotic and eukaryotic organisms. Thus, when expressing a prokaryotic protein such as a clostridial neurotoxin, in a eukaryotic expression system, it may be necessary, or at least helpful, to adapt the nucleic acid sequence to the codon usage of the expression host cell, meaning that sequence identity or homology may be rather low on the nucleic acid level.

[00111] In the context of the present invention, the term "variant" refers to a neurotoxin that is a chemically, enzymatically, or genetically modified derivative of a parental clostridial neurotoxin. A chemically modified derivative may be one that is

modified by pyruvation, phosphorylation, sulfatation, lipidation, pegylation, glycosylation and/or the chemical addition of an amino acid or a polypeptide comprising between 2 and 100 amino acids, including modification occurring in the eukaryotic host cell used for expressing the derivative. An enzymatically modified derivative is one that is modified by the activity of enzymes, such as endo- or exoproteolytic enzymes, including modification by enzymes of the eukaryotic host cell used for expressing the derivative. As pointed out above, a genetically modified derivative is one that has been modified by deletion or substitution of one or more amino acids contained in, or by addition of one or more amino acids (including polypeptides comprising between 2 and about 100 amino acids) to, the amino acid sequence of said parental clostridial neurotoxin. Methods for designing and constructing such chemically or genetically modified derivatives and for testing of such variants for functionality are well known to anyone of ordinary skill in the art.

[00112] In the context of the present invention, the term “recombinant neurotoxin” refers to a composition comprising a clostridial neurotoxin that is obtained by expression of the neurotoxin in a heterologous cell such as *E. coli*, and including, but not limited to, the raw material obtained from a fermentation process (supernatant, composition after cell lysis), a fraction comprising a clostridial neurotoxin obtained from separating the ingredients of such a raw material in a purification process, an isolated and essentially pure protein, and a formulation for pharmaceutical and/or aesthetic use comprising a clostridial neurotoxin and additionally pharmaceutically acceptable solvents and/or excipients.

[00113] In the context of the present invention, the term “comprises” or “comprising” means “including, but not limited to”. The term is intended to be open-ended, to specify the presence of any stated features, elements, integers, steps or components, but not to preclude the presence or addition of one or more other features, elements, integers, steps, components, or groups thereof. The term “comprising” thus includes the more restrictive terms “consisting of” and “consisting essentially of”.

[00114] Clostridial neurotoxins display variable durations of action that are serotype specific. The clinical therapeutic effect of BoNT/A lasts approximately 3 months for neuromuscular disorders and 6 to 12 months for hyperhidrosis. The effects of BoNT/E, on the other hand, last about 4 weeks. One possible explanation for the divergent durations of action might be the distinct subcellular localizations of BoNT serotypes. The protease domain of BoNT/A light chain localizes in a punctate manner to the plasma membrane of neuronal cells, co-localizing with its substrate SNAP-25. In contrast, the short-duration BoNT/E serotype is cytoplasmic. Membrane association might protect BoNT/A from cytosolic degradation mechanisms allowing for prolonged persistence of BoNT/A in the neuronal cell.

[00115] The longer lasting therapeutic effect of BoNT/A makes it preferable for certain clinical uses and in particular for certain cosmetic uses compared to the other serotypes, for example serotypes B, C₁, D, E, F, G and H.

[00116] In certain cases, it might be advantageous to further increase the duration of the therapeutic effect of a botulinum neurotoxin in order to increase the duration of muscle paralysis. In particular such cases, variants of BoNT/A as described in WO 2007/104567, WO 2010/022979, or WO 2014/086494 may be used. Examples of particularly suitable botulinum neurotoxins are disclosed in WO2015/132004. These modified botulinum neurotoxins are based on the addition of at least one domain comprising an amino acid sequence comprises a plurality of amino acid repeats of at least 50 amino acid residues, wherein the amino acid residues are selected from proline, alanine and serine residues (PAS sequence).

[00117] On the other hand, it might be advantageous in certain scenarios to further decrease the duration of the therapeutic effect of a botulinum neurotoxin in order to reduce the duration of muscle paralysis. A naturally occurring clostridial toxin with reduced duration of therapeutic effect is BoNT/E, which is available using recombinant expression from E.coli using the procedures disclosed in WO 2014/068317. In particular such cases, artificial variants of BoNT/E as described in WO 2011/000929 or WO 2013/068476 may be used. In brief, the applications describe polypeptides comprising at least one E3 ligase recognition motif in the light

chain, wherein said E3 ligase recognition motif is preferably a binding motif for the E3 ligase MDM2.

[00118] In particular, WO 2013/068476 describes variants of BoNT/E (SEQ ID NOs: 52 and 80 in WO 2013/068476), which were shown to have a duration of effect, which was decreased by about 25% compared to wild-type BoNT/E in a cell culture assay with an onset of effect within a day and an estimated duration of effect of 4 weeks ($\pm$ 2 weeks) Thus, in particular embodiments, a neurotoxic component of a Botulinum toxin according to SEQ ID NO: 9 or SEQ ID NO: 10 is used.

[00119] In particular embodiments, in step (i) from 1 to 6 U of the neurotoxic component of Botulinum toxin are injected into each of between 1 and 30 different points of said tissue.

[00120] In particular embodiments, said tissue is selected from platysma, frown line, marionette line, and décolletage, in particular platysma.

[00121] In particular embodiments, in step (i) 30 – 60 U of the neurotoxic component of Botulinum toxin are injected superficially by injection of between 1 and 2 U into each of 15-30 points of the skin of the platysma.

[00122] In particular embodiments, said treatment further comprises the step of (ii) applying ultrasound to the tissue treated with said clostridial neurotoxin.

[00123] The application of ultrasound to tissue as a nonsurgical way to lift, tone and tighten skin is known in the art, for example under the tradename Ultherapy® (see Brobst et al., Ulthera: initial and six month results. Facial Plast Surg Clin North Am. 2012 May;20(2):163-76).

[00124] According to an internet search performed in October 2015, the combination of a botulinum toxin-based treatment and Ultherapy® has been discussed and/or applied by certain practitioners in the field of cosmetic treatments, including a combination with additional use of fillers (“Ultherapy Plus” according to

David Loh). While it is mentioned that both approaches are compatible, so that they can be combined concurrently or consecutively, there are not reports or data on particular advantages obtained by such combination approach.

[00125] Surprisingly, the present inventors present that a pre-treatment of a muscle tissue with high muscle tension with a clostridial neurotoxin results in a relaxation of the muscle tissue, which strongly improves the healing and collagenisation process following a subsequent application of ultrasound as part of an Ultherapy[®] process.

[00126] In the context of the present invention, the term "pre-treatment" refers to a combined treatment of applying a clostridial neurotoxin and ultrasound, wherein step i) precedes step ii). There are no specific limitations regarding the period of time between step i) and step ii) in the treatment according to the present invention as long as the treatments in step i) and step ii) can interact with each other. In accordance with the present invention, step ii) may be scheduled at least one day after preceding preceeding step i). The term "at least one day after" means e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 weeks. However, it is also envisaged by the teaching of the present invention that step ii) is scheduled only few hours after step i), e.g. 2, 3, 4, 5, 6, 7 or 8 hours later.

[00127] In another embodiment the present invention refers to a combined treatment wherein the clostridial toxin is administered at least one day after the application of ultrasound, i.e. step ii) precedes step i). The term "at least one day after" means e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 weeks. However, it is also envisaged by the teaching of the present invention that step i) is scheduled only few hours after step ii), e.g. 2, 3, 4, 5, 6, 7 or 8 hours later.

[00128] In the context of the present invention, the term "Ultherapy[®]" refers to a process that is an ultrasound therapy, which is protected and FDA-approved CE certificated for specific indications.

[00129] In one embodiment the ultrasound treatment which is used within the method of the present invention as step (ii) is disclosed in WO 2006/042168,

WO 2006/042201 and WO 2009/149390. In a particular embodiment, the ultrasound treatment which is used within the method of the present invention as step (ii) is disclosed in PCT/US2015/025581 published on October 14, 2015.

[00130] In brief, the ultrasound treatment uses ultrasound devices having a transducer probe operable to emit and receive ultrasound energy for cosmetic treatment and imaging.

[00131] In particular embodiments, the ultrasound treatment employs a system and method for cosmetic treatment and imaging.

[00132] In particular embodiments, said ultrasound is applied to heat a treatment area in said tissue at the focal depth to a temperature in a range between 40 - 65°C.

[00133] In particular embodiments, in step (ii), ultrasound is applied to said tissue by selecting one or more areas in said tissue, particularly one or more areas with between 4 and 9 cm², particularly squares of between 4 and 9 cm², particularly squares with 6.25 cm². In particular embodiments, in step (ii), ultrasound is applied in one or more lines in each of said one or more areas, in particular in between 5 and 30 lines. In particular embodiments, in step (ii), high-frequency ultrasound (i.e. 1 MHz or above) is applied, particularly ultrasound at a frequency between 1 and 12 MHz, particularly between 3 and 12 MHz, particularly between 4 and 10 MHz, particularly selected from 4, 7 and 10 MHz. In particular embodiments, in step (ii), ultrasound is applied with a focal depth of between 1 and 5 mm, particularly between 1.5 and 4.5 mm, particularly selected from 1.5 mm, 3 mm and 4.5 mm.

[00134] In particular embodiments, said lines are applied by moving an ultrasound transducer along the direction of said lines.

[00135] In particular such embodiments, said lines are applied by using the set of conditions as shown in Table 2, part A.

[00136] In particular other embodiments, in step (ii) an ultrasound transduction system is used, comprising: a cylindrical transduction element; and a power source configured to drive the cylindrical transduction element, wherein the cylindrical transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth.

[00137] Thus, the present invention relates in a particular aspect to clostridial neurotoxin for use in the treatment of a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, wherein said treatment comprises the steps of (i) applying said clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of the body associated with high muscle tension; and (ii) applying ultrasound to the tissue treated with said clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used that is configured to apply ultrasonic energy to a linear focal zone at a focal depth

[00138] In a particular embodiment, the present invention relates to a clostridial neurotoxin for use in the treatment of a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, wherein said treatment comprises the steps of (i) applying said clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of the body associated with high muscle tension; and (ii) applying ultrasound to the tissue treated with said clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used, comprising: a cylindrical transduction element; and a power source configured to drive the cylindrical transduction element, wherein the cylindrical transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth.

[00139] In a second aspect the present invention relates to a method of treating a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, comprising the steps of (i) applying a clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of said tissue associated with high muscle tension; and (ii) applying ultrasound to the tissue treated with said

clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used that is configured to apply ultrasonic energy to a linear focal zone at a focal depth.

[00140] In a particular embodiment, the present invention relates to a method of treating a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, comprising the steps of (i) applying a clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of said tissue associated with high muscle tension; and (ii) applying ultrasound to the tissue treated with said clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used, comprising: a cylindrical transduction element; and a power source configured to drive the cylindrical transduction element, wherein the cylindrical transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth.

[00141] In particular such embodiments, said cylindrical transduction element comprises a first surface and a second surface, wherein the first surface comprises an electrically conductive coating, herein the second surface comprises at least one electrically conductive coated region and at least one region that is not coated with an electrically conductive coating, wherein the at least one coated region on the second surface comprises a conductive material that forms an electrode when the power source is in electric communication with the at least one coated region, wherein the at least one coated region on the second surface is configured to reduce edge noise at the linear focal zone at the focal depth.

[00142] In particular embodiments, the cylindrical transduction element further comprises one or more imaging elements, wherein the cylindrical transduction element has an opening configured for placement of the one or more imaging elements, wherein the cylindrical transduction element is housed within an ultrasonic hand-held probe, wherein the ultrasonic probe comprises: a housing, the cylindrical transduction element, and a motion mechanism; wherein the ultrasound transducer is movable within the housing, wherein the motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a

linear path within the housing, wherein the conductive material is silver, wherein the first surface is a concave surface and the second surface is a convex surface.

[00143] In particular such embodiments, said first surface is a concave surface and the second surface is a convex surface.

[00144] In particular other embodiments, said first surface is a convex surface and the second surface is a concave surface.

[00145] In particular embodiments, said cylindrical transduction element is housed within an ultrasonic hand-held probe, wherein the ultrasonic probe comprises: a housing, the cylindrical transduction element, and motion mechanism; wherein the ultrasound transducer is movable within the housing, wherein the motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing.

[00146] In particular embodiments, said motion mechanism automatically moves the cylindrical transduction element to heat a treatment area at the focal depth to a temperature in a range between 40 - 65°C.

[00147] In particular embodiments, said reduction of edge noise facilitates the production of a uniform temperature in a treatment area.

[00148] In particular embodiments, said reduction of edge noise facilitates the efficient and consistent treatment of a tissue, wherein the cylindrical transduction element is configured to apply ultrasonic therapy to a treatment zone at the focal depth in the tissue.

[00149] In particular embodiments, said reduction of edge noise reduces a peak such that a variance around the focal depth is reduced by 75 - 200%.

[00150] In particular embodiments, said reduction of edge noise reduces a peak such that a variance of intensity around the focal depth is 5 mm or less.

[00151] In particular embodiments, said reduction of edge noise reduces a variance in focal gain in a range of 0.01 - 10.

[00152] In particular embodiments, said power source is configured to drive the cylindrical transduction element to produce a temperature in a range of 42 - 55°C in a tissue at the focal depth.

[00153] In particular embodiments, the cylindrical transduction element further comprises a temperature sensor located on the housing proximate an acoustic window in the housing configured to measure a temperature at a skin surface.

[00154] In particular embodiments, the cylindrical transduction element further comprises one or more imaging elements, wherein the cylindrical transduction element has an opening configured for placement of the one or more imaging elements.

[00155] In particular embodiments, said imaging element is configured to confirm a level of acoustic coupling between the system and a skin surface.

[00156] In particular embodiments, said imaging element is configured to confirm a level of acoustic coupling between the system and a skin surface via any one of the group consisting of: defocused imaging and Voltage Standing Wave Ratio (VSWR).

[00157] In particular embodiments, said imaging element is configured to measure a temperature at a target tissue at the focal depth below a skin surface.

[00158] In particular embodiments, said imaging element is configured to measure a temperature at a target tissue at the focal depth below a skin surface with any one of the group of Acoustic Radiation Force Impulse (ARFI), Shear Wave Elasticity Imaging (SWEI), and measurement of attenuation.

[00159] In particular other embodiments, said step (ii) comprises the step of providing a cylindrical transduction element comprising a first surface, a second surface, a coated region, and an uncoated region, wherein the coated region comprises an electrical conductor, wherein the first surface comprises at least one coated region, wherein the second surface comprises the uncoated region and a plurality of coated regions, applying a current to the coated region, thereby directing ultrasound energy to a linear focal zone at a focal depth, wherein the ultrasound energy produces a reduction in focal gain at the linear focal zone.

[00160] In particular embodiments, said reduction of focal gain facilitates the efficient and consistent treatment of tissue, wherein the cylindrical transduction element is configured to apply ultrasonic therapy to a thermal treatment zone at a focal depth.

[00161] In particular embodiments, said reduction of focal gain reduces a peak such that a variance around the focal depth is reduced by 25 - 100%.

[00162] In particular embodiments, said reduction of focal gain reduces a peak such that a variance of intensity around the focal depth is 5 mm or less.

[00163] In particular embodiments, said reduction of focal gain reduces a variance in focal gain in a range of 0.01 - 10.

[00164] In particular embodiments, said electrical conductor is a metal.

[00165] In particular embodiments, said first surface is a concave surface and the second surface is a convex surface.

[00166] In particular other embodiments, said first surface is a convex surface and the second surface is a concave surface.

[00167] In particular embodiments, said cylindrical transduction element is housed within an ultrasonic hand-held probe, wherein the ultrasonic probe

comprises: a housing, the cylindrical transduction element, and a motion mechanism; wherein the ultrasound transducer is movable within the housing, wherein the motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing.

[00168] In particular other embodiments, said motion mechanism automatically moves the cylindrical transduction element to heat a treatment area at the focal depth to a temperature in a range between 40 - 65°C.

[00169] In particular other embodiments, said the cylindrical transduction element produces a temperature in a range of 42 - 55°C in a tissue at the focal depth.

[00170] In particular embodiments, the cylindrical transduction element further comprises imaging tissue with one or more imaging elements, wherein the cylindrical transduction element has an opening configured for placement of the one or more imaging elements.

[00171] In particular embodiments, the cylindrical transduction element further comprises confirming a level of acoustic coupling between the system and a skin surface with an image from the imaging element.

[00172] In particular embodiments, the cylindrical transduction element further comprises confirming a level of acoustic coupling between the system and a skin surface with the imaging element using any one of the group consisting of: defocused imaging and Voltage Standing Wave Ratio (VSWR).

[00173] In particular embodiments, the cylindrical transduction element further comprises measuring a temperature at a target tissue at the focal depth below a skin surface with the imaging element.

[00174] In particular embodiments, the cylindrical transduction element further comprises measuring a temperature with the imaging element at a target tissue at the focal depth below a skin surface with any one of the group of Acoustic Radiation

Force Impulse (ARFI), Shear Wave Elasticity Imaging (SWEI), and measurement of attenuation.

[00175] In particular embodiments, said treatment is a non-invasive, cosmetic method of heating tissue comprising the step of applying a cosmetic heating system to a skin surface, wherein the cosmetic heating system comprises a hand-held probe, wherein the hand-held probe comprises a housing that encloses an ultrasound transducer configured to heat tissue below the skin surface to a tissue temperature in the range of 40 - 50°C, wherein the ultrasound transducer comprises a cylindrical transduction element comprising a first surface, a second surface, a coated region, and an uncoated region, wherein the coated region comprises an electrical conductor, wherein the first surface comprises at least one coated region, wherein the second surface comprises the uncoated region and a plurality of coated regions, applying a current to the plurality of coated regions, thereby directing ultrasound energy to a linear focal zone at a focal depth, wherein the ultrasound energy produces a reduction in focal gain at the linear focal zone, thereby heating the tissue at the focal depth in the linear focal zone to the tissue temperature in the range of 40 - 50°C for a cosmetic treatment duration of less than 1 hour, thereby reducing a volume of an adipose tissue in the tissue.

[00176] In particular embodiments, said reduction of focal gain facilitates the efficient and consistent treatment of tissue, wherein the cylindrical transduction element is configured to apply ultrasonic therapy to a thermal treatment zone at a focal depth.

[00177] In particular embodiments, said reduction of focal gain reduces a peak such that a variance around the focal depth is reduced by 25 - 100%.

[00178] In particular embodiments, said reduction of focal gain reduces a peak such that a variance of intensity around the focal depth is 5 mm or less.

[00179] In particular embodiments, said reduction of focal gain reduces a variance in focal gain in a range of 0.01 - 10.

[00180] In particular embodiments, said electrical conductor is a metal.

[00181] In particular embodiments, said first surface is a concave surface and the second surface is a convex surface.

[00182] In particular other embodiments, said first surface is a convex surface and the second surface is a concave surface.

[00183] In particular embodiments, said cylindrical transduction element is housed within an ultrasonic hand-held probe, wherein the ultrasonic probe comprises: a housing, the cylindrical transduction element, and a motion mechanism; wherein the ultrasound transducer is movable within the housing, wherein the motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing.

[00184] In particular embodiments, said motion mechanism automatically moves the cylindrical transduction element to heat a treatment area at the focal depth to a temperature in a range between 40 - 65°C.

[00185] In particular embodiments, said cylindrical transduction element produces a temperature in a range of 42 - 55°C in a tissue at the focal depth.

[00186] In particular embodiments, the cylindrical transduction element further comprises imaging tissue with one or more imaging elements, wherein the cylindrical transduction element has an opening configured for placement of the one or more imaging elements.

[00187] In particular embodiments, the cylindrical transduction element further comprises confirming a level of acoustic coupling between the system and a skin surface with an image from the imaging element.

[00188] In particular embodiments, the cylindrical transduction element further comprises confirming a level of acoustic coupling between the system and a skin surface with the imaging element using any one of the group consisting of: defocused imaging and Voltage Standing Wave Ratio (VSWR).

[00189] In particular embodiments, the cylindrical transduction element further comprises measuring a temperature at a target tissue at the focal depth below a skin surface with the imaging element.

[00190] In particular embodiments, the cylindrical transduction element further comprises measuring a temperature with the imaging element at a target tissue at the focal depth below a skin surface with any one of the group of Acoustic Radiation Force Impulse (ARFI), Shear Wave Elasticity Imaging (SWEI), and measurement of attenuation.

[00191] In particular embodiments, the treatment system includes a hand wand with at least one finger activated control, or controller, and a removable transducer module having at least one ultrasound transducer. In particular embodiments, the system includes a control module that is coupled to the hand wand and has a graphic user interface for controlling the removable transducer module that has an interface coupling the hand wand to the control module. The transducer module may further comprise at least one interface that can be coupled to the hand wand.

[00192] In particular embodiments, particularly for use in cosmetic treatment, the wand includes a first controlling device operably controlling an imaging function, a second controlling device operably controlling a treatment function, a status indicator, an input for power, an output for at least one signal, a movement mechanism and a removable transducer module operably coupled to at least one of the first controlling device, the second controlling device and the movement mechanism.

[00193] In particular embodiments, particularly of a method of performing cosmetic treatment on a facial (or other) area of a subject, the method includes inserting a transducer module into a hand controller, coupling the transducer module

to the subject, activating a first switch on the hand controller operably initiating an imaging sequence of a portion of tissue below the dermal layer, collecting data from the imaging sequence, calculating a treatment sequence from the data, and activating a second switch on the hand controller operably initiating the treatment sequence.

[00194] In particular embodiments, the method also includes emitting a first ultrasound energy from a first transducer in the transducer module operably providing a source for the imaging sequence. In particular embodiments, the method also includes emitting a second ultrasound energy from a second transducer in the transducer module operably providing a source for the treatment sequence.

[00195] In particular embodiments, the method also includes tightening a portion of the dermal layer on a facial area of a subject.

[00196] In particular embodiments, the method provides for the transducer module to permit the treatment sequence at a fixed depth below the dermal layer. In particular embodiments, the hand wand includes a first controlling device operably controlling an ultrasonic imaging function, a second controlling device operably controlling an ultrasonic treatment function, a movement mechanism configured for travel through a liquid-tight seal, and a fluid-filled transducer module. In particular embodiments, the linear sequence of individual thermal lesions has a treatment spacing in a range from about 0.01 mm to about 25 mm. In particular embodiments, the ultrasonic parameter can relate to transducer geometry, size, timing, spatial configuration, frequency, variations in spatial parameters, variations in temporal parameters, coagulation formation, depth, width, absorption coefficient, refraction coefficient, tissue depths, and/or other tissue characteristics. In particular embodiments, the removable transducer modules can be configured for a tissue depth of 3 mm, 4.5 mm, 6 mm, less than 3 mm, between 3 mm and 4.5 mm, more than more than 4.5 mm, more than 6 mm, and anywhere in the ranges of 0-3 mm, 0-4.5 mm, 0-25 mm, 0-100 mm, and any depths therein.

[00197] In particular embodiments, a method of treating the lower face and neck area (e.g., the submental area) is provided. In several embodiments, a method of

treating (e.g., softening) mentolabial folds is provided. In particular embodiments, a method of treating the eye region is provided. Upper lid laxity improvement and periorbital lines and texture improvement will be achieved by several embodiments by treating at variable depths.

[00198] In particular embodiments, a variable ultrasonic parameter system is provided, particularly for use in cosmetic treatment, wherein the system includes a first controlling device, a second controlling device, a movement mechanism, a first removable transducer module and a second removable transducer module. The first controlling device operably controls an ultrasonic imaging function. The second controlling device operably controls an ultrasonic treatment function. The movement mechanism is configured to create a linear sequence of individual thermal lesions for treatment purposes.

[00199] In particular embodiments, particularly for use in cosmetic treatment, the hand wand comprises a first controlling device, a second controlling device, a movement mechanism, and a transducer module. The first controlling device operably controls an ultrasonic imaging function for providing ultrasonic imaging. The second controlling device operably controls an ultrasonic treatment function for providing ultrasonic treatment. The movement mechanism is configured to direct ultrasonic treatment in a sequence of individual thermal lesions.

[00200] In a second embodiment the ultrasound treatment used as step (ii) in the method of the present invention relates to using band shaped treatment focus zone techniques to expand the area and volume of tissue treated at a specific, targeted area.

[00201] Although energy-based treatments have been disclosed for cosmetic and medical purposes, no procedures are known to Applicant, other than Applicant's own work, that successfully achieve an aesthetic tissue heating and/or treatment effect using targeted and precise ultrasound to cause a visible and effective cosmetic results via a thermal pathway by using band shaped treatment focus zone techniques to expand the area and volume of tissue treated at a specific, targeted area.

Treatment can include heating, coagulation, and/or ablation (including, for example, hyperthermia, thermal dosimetry, apoptosis, and lysis). In various embodiments, band treatment provides improved thermal heating and treatment of tissue compared to diathermy or general bulk heating techniques. In various embodiments, band treatment provides the capability of heating and/or treating tissue at specific depth ranges without affecting proximal tissues. In general, diathermy and bulk heating techniques usually involve heating a skin surface and conducting the heat through the skin surface and all underlying tissue to reach a tissue at a target depth below the skin surface. In various embodiments, band treatment provides targeted heating and treatment at a specific, prescribed depth range below the skin surface without heating the skin surface and/or intermediary tissue between the skin surface and the target tissue. This offset band treatment reduces damage and associated pain at the skin surface, and treats tissue only at the prescribed, targeted tissue depth. Thus, embodiments of the present invention can be used to treat tissue in a specific range of depths below the skin surface without heating the skin surface. In some embodiments, band treatment can also be used to prepare tissue at target depths for a second, ultrasound treatment by pre-heating the target tissue to an elevated temperature so the secondary treatment can be performed with reduced time and/or energy and increased comfort.

[00202] In accordance with various embodiments, a cosmetic ultrasound treatment system and/or method can non-invasively produce single or multiple cosmetic treatment zones and/or thermal treatment points, lines, bands, belts, planes, areas, volumes, and/or shapes, where ultrasound is focused in one or more locations in a region of treatment in tissue at one or more depths under a skin surface. Some systems and methods provide cosmetic treatment at different locations in tissue, with treatment areas at various depths, heights, widths, and/or positions. In one embodiment, a method and system comprise a transducer system configured for providing ultrasound treatment to more than one region of interest, such as between at least two treatment positions and/or regions of interest. In one embodiment, a method and system comprise a transducer system configured for providing ultrasound treatment to more than one region of interest, such as between at least two lines in various locations (e.g. at a fixed or variable depth, height, width,

orientation, etc.) in a region of interest in tissue. In various embodiments, lines can be straight, curved, continuous, and/or non-continuous. In some embodiments, the energy beam is split to focus at two, three, four, or more focal zones (e.g., multiple focal lines, multi-focal lines) for cosmetic treatment zones and/or for imaging in a region of interest in tissue. Position of the focal zones can be positioned axially, laterally, or otherwise within the tissue. Some embodiments can be configured for spatial control, such as by the location of a focus line, changing the distance or angle between a transducer and an optional motion mechanism, and/or changing the angles of energy focused or unfocused to the region of interest, and/or configured for temporal control, such as by controlling changes in the frequency, drive amplitude and timing of the transducer. In some embodiments the position of multiple treatment zones can be enabled through poling, phasic poling, biphasic poling, and/or multi-phasic poling. As a result, changes in the location of the treatment region, the number, shape, size and/or volume of treatment zones, heating zones, and/or lesions in a region of interest, as well as the thermal conditions, can be dynamically controlled over time. Additional details regarding poling and modulation are disclosed in U.S. Application No. 14/193,234 filed on February 28, 2014 and published as U.S. Publication No. 2014-0257145, which is incorporated in its entirety by reference herein.

[00203] In one embodiment, an aesthetic imaging and treatment system includes a hand held probe with a housing that encloses an ultrasound transducer configured to apply ultrasound therapy to tissue at a focal zone. In one embodiment, the focal zone is a line. In one embodiment, the focal zone is a two dimensional region or plane. In one embodiment, the focal zone is a volume. In various embodiments, the focal zone treats a treatment area that is linear, curved, rectangular, and/or planar. In various embodiments, the size of the treatment area depends on the size of the transducer. The treatment can be performed in lines and/or planes. In various embodiments, the width of the treatment focal zone is 5 - 50 mm, 5 - 30 mm, 5 - 25 mm, 10 - 25 mm, 10 mm - 15 mm, 15 mm - 20 mm, 10 mm, 15 mm, 20 mm, 25 mm, or any range therein (including but not limited to 12 mm - 22 mm). In various embodiments, a focal zone can be moved to sweep a volume between a first position and a second position. In various embodiments, one or more

a focal zone locations are positioned in a substantially linear sequence within a cosmetic treatment zone. In various embodiments, one or more a focal zone locations are positioned with one, two, or more motion mechanisms to form any shape for a treatment area within a cosmetic treatment zone. In one embodiment, a first set of locations is positioned within a first cosmetic treatment zone and a second set of locations is positioned within a second cosmetic treatment zone, the first zone being different from the second zone. In one embodiment, the first cosmetic treatment zone includes a substantially linear sequence of the first set of locations and the second cosmetic treatment zone includes a substantially linear sequence of the second set of locations. In some non-limiting embodiments transducers can be configured for a treatment zone at a tissue depth below a skin surface of 1.5 mm, 3 mm, 4.5 mm, 6 mm, less than 3 mm, between 1.5 mm and 3 mm, between 1.5 mm and 4.5 mm, more than more than 4.5 mm, more than 6 mm, and anywhere in the ranges of 0.1 mm - 3 mm, 0.1 mm - 4.5 mm, 3 mm - 7 mm, 3 mm - 9 mm, 0.1 mm - 25 mm, 0.1 mm - 100 mm, and any depths therein (including, for example, 4.5 mm - 6 mm, 1 mm - 20 mm, 1 mm - 15 mm, 1 mm - 10 mm, 5 mm - 25 mm, and any depths therein). In one embodiment, cosmetic treatment zones are continuous. In one embodiment, cosmetic treatment zones have no spacing. In one embodiment, a sequence of individual cosmetic treatment zones with a treatment spacing in a range from about 0.05 mm to about 25 mm (e.g., 0.05 - 0.1 mm, 0.05 - 1 mm, 0.2 - 0.5 mm, 0.5 - 2 mm, 1 - 10 mm, 0.5 - 3 mm, 5 - 12 mm). In various embodiments, the treatment spacing has a constant pitch, a variable pitch, an overlapping pitch, and/or a non-overlapping pitch.

[00204] In one embodiment, the ultrasonic transducer is configured to provide therapeutic intensity on the transducer surface in a range of between about 1 W/cm² to 100 W/cm² (e.g., 1 - 50, 10 - 90, 25 - 75, 10 - 40, 50 - 80 W/cm² and any ranges and values therein). In one embodiment, the ultrasonic transducer is configured to provide an acoustic power of the ultrasonic therapy in a range of between about 1 W to about 100 W and a frequency of about 1 MHz to about 10 MHz to thermally heat the tissue. In various embodiments, the transducer module is configured to provide an acoustic power of the ultrasonic therapy in a range of between about 1 W to about 100 W (e.g., 5 - 40 W, 10 - 50 W, 25 - 35 W, 35 - 60 W, 35 W, 40 W, 50 W, 60 W)

and a frequency of about 1 MHz to about 10 MHz to thermally heat the tissue. In one embodiment, the acoustic power can be from a range of 1 W to about 100 W in a frequency range from about 1 MHz to about 12 MHz (e.g., 3.5 MHz, 4 MHz, 4.5 MHz, 7 MHz, 10 MHz, 3 - 5MHz), or from about 10 W to about 50 W at a frequency range from about 3 MHz to about 8 MHz. In one embodiment, the acoustic power and frequencies are about 40 W at about 4.3 MHz and about 30 W at about 7.5 MHz. In various embodiments, the transducer module is configured to deliver energy with no pitch or a pitch of 0.1 - 2 mm (e.g., 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.5 mm). In various embodiments, the pitch is constant or variable. In various embodiments, the transducer module is configured to deliver energy with an on-time of 10 - 500 ms (e.g., 30 - 100, 90 - 200, 30, 32, 35, 40, 50, 60, 64, 75, 90, 100, 112, 200, 300, 400 ms and any range therein). In various embodiments, the transducer module is configured to deliver energy with an off-time of 1- 200 ms (e.g., 4, 10, 22, 45, 60, 90, 100, 150 ms and any range therein). In one embodiment, an acoustic energy produced by this acoustic power can be between about 0.01 joule ("J") to about 10 J or about 2 J to about 5 J. In one embodiment, the acoustic energy is in a range less than about 3 J. In various embodiments, an acoustic energy produced by this acoustic power in a single dose pass can be between about 1 - 500 J (e.g., 20 - 310, 70, 100, 120, 140, 150, 160, 200, 250, 300, 350, 400, 450 J and any range therein). In various embodiments, a treatment can involve 1, 2, 3, 4, 5, 10 or more dose passes.

[00205] In several embodiments disclosed herein, non-invasive ultrasound is used to achieve one or more of the following effects: tissue heating, tissue pre-heating, a face lift, a brow lift, a chin lift, an eye treatment, a wrinkle reduction, a scar reduction, a burn treatment, a tattoo removal, a vein removal, a vein reduction, a treatment on a sweat gland, a treatment of hyperhidrosis, a fat or adipose and/or cellulite reduction, a sun spot removal, an acne treatment, a pimple reduction. Treatment of the décolletage is provided in several embodiments. In another embodiment the system, device and/or method may be applied in the genital area (e.g., vaginal rejuvenation and/or vaginal tightening, such as for tightening the supportive tissue of the vagina). In several of the embodiments described herein, the procedure is entirely cosmetic and not a medical act. For example, in one

embodiment, the methods described herein need not be performed by a doctor, but at a spa or other aesthetic institute. In some embodiments, a system can be used for the non-invasive cosmetic treatment of skin.

[00206] In one embodiment, a method of reducing variance in focal gain of a cylindrical ultrasound transducer includes providing a cylindrical transduction element comprising a convex surface and a concave surface, wherein one of the surfaces (e.g., the concave surface) comprises a plurality of electrodes (or e.g., electrical conductor or electrical material), and subsequently applying a current to the electrode, thereby directing ultrasound energy to a linear focal zone at a focal depth. The ultrasound energy produces a reduced variance in focal gain at the linear focal zone. The concave surface can be plated with silver. The convex surface can include an uncoated region and a plurality of coated regions. The plurality of coated regions can include fired silver to form the plurality of electrodes. The features on the convex surface can instead be on the concave surface.

[00207] In one embodiment, the reduction of edge noise facilitates the efficient and consistent treatment of tissue, wherein the cylindrical transduction element is configured to apply ultrasonic therapy to a linear tissue thermal treatment zone at a focal depth.

[00208] In one embodiment, the reduction of edge noise facilitates the efficient and consistent heating of a material, wherein the material is any one of the group consisting of a compound, an adhesive, and food.

[00209] In one embodiment, an ultrasound transduction system for reducing edge noise at a focal line includes a cylindrical transduction element and a power source configured to drive the cylindrical transduction element. The cylindrical transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth. The cylindrical transduction element includes a convex surface and a concave surface. The concave surface is plated with an electrical conductor, such as silver. The convex surface includes an uncoated region and one or more coated regions, wherein the one or more coated regions include silver to form an electrode.

The power source is in electric communication with the electrode. The coated regions are configured to reduce variance in focal gain at the linear focal zone at the focal depth.

[00210] In one embodiment, an ultrasound transduction system for reducing edge noise at a focal line includes a cylindrical transduction element and a power source configured to drive the cylindrical transduction element. The cylindrical transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth. The cylindrical transduction element includes a convex surface and a concave surface. The convex surface plated with silver. The concave surface includes an uncoated region and one or more coated regions, wherein the one or more coated regions include silver to form an electrode. The power source is in electric communication with the electrode. The coated regions are configured to reduce variance in focal gain at the linear focal zone at the focal depth.

[00211] In one embodiment, a coated transducer for reducing variance in focal gain at a focal zone includes a cylindrical transduction element comprising a convex surface and a concave surface. The concave surface is plated with silver. The convex surface includes an uncoated region and a plurality of coated regions. The plurality of coated regions includes silver to form a plurality of electrodes. The cylindrical transduction element is configured to apply ultrasonic therapy to a linear focal zone at a focal depth. The coated regions are configured to reduce variance in focal gain at the linear focal zone.

[00212] In one embodiment, a coated transducer for reducing variance in focal gain at a focal zone includes a cylindrical transduction element comprising a convex surface and a concave surface. In one embodiment the convex surface is plated. In one embodiment the concave surface is plated. In one embodiment the concave surface includes an uncoated region and a plurality of coated regions. In one embodiment the convex surface includes an uncoated region and a plurality of coated regions. The plurality of coated regions includes a conductor to form a plurality of electrodes. The cylindrical transduction element is configured to apply

ultrasonic therapy to a linear focal zone at a focal depth. The coated regions are configured to reduce variance in focal gain at the linear focal zone.

[00213] In one embodiment, an aesthetic treatment system includes a cylindrical transduction element comprising a convex surface and a concave surface. In one embodiment the concave surface is plated with silver to form an electrode. In one embodiment the convex surface is plated with silver to form an electrode. In one embodiment the convex surface includes an uncoated region and one or more coated regions, wherein the one or more coated regions include silver to form an electrode. In one embodiment the concave surface includes an uncoated region and one or more coated regions, wherein the one or more coated regions include silver to form an electrode. The cylindrical transduction element is configured to apply ultrasonic therapy to a linear tissue thermal treatment zone at a focal depth. The coated regions are configured to reduce variance in focal gain at the thermal treatment zone. The cylindrical transduction element is housed within an ultrasonic hand-held probe. In one embodiment, the ultrasonic probe includes a housing, the cylindrical transduction element, and a motion mechanism. The ultrasound transducer is movable within the housing. The motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing.

[00214] In one embodiment, an aesthetic imaging and treatment system includes an ultrasonic probe that includes a housing, a coated ultrasound transducer, and a motion mechanism. The ultrasound transducer is movable within the housing, the ultrasound transducer including a cylindrical transduction element and an imaging element. The cylindrical transduction element is configured to apply ultrasonic therapy to a linear tissue thermal treatment zone at a focal depth. The cylindrical transduction element has an opening configured for placement of the imaging element. The cylindrical transduction element includes a convex surface and a concave surface. In one embodiment, the entire concave surface is plated with silver. In one embodiment, the entire convex surface is plated with silver. In one embodiment, the convex surface includes an uncoated portion and one or more coated regions. In one embodiment, the concave surface includes an uncoated

portion and one or more coated regions. The coated region includes silver to form an electrode. The coated regions are configured to reduce variance in focal gain at the thermal treatment zone. The motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing.

[00215] As provided herein, one of the surfaces of the transduction element (either the convex or the concave surface) is fully coated (or at least 90% coated) with an electrically conductive material (including but not limited to silver or another metal or alloy) and the other surface (either the convex or the concave surface) has regions (or a pattern or patchwork) of coated and uncoated portions that are coated with an electrically conductive material (including but not limited to silver or another metal or alloy). This, in several embodiments, can be advantageous because it facilitates uniform heating (e.g., reducing temperature spikes or fluctuations). In some embodiments, both surfaces (convex and concave surfaces) contain regions (or a pattern or patchwork) of coated and uncoated portions. Although convex and concave surfaces are described herein, one or both of these surfaces may be planar in some embodiments. Additionally, convex or concave surfaces as described herein may be multi-faceted (e.g., with multiple convexities and/or concavities) and also include surfaces with a curvature (e.g., one or more angles less than 180 degrees). In several embodiments, the pattern of coated and uncoated regions can include one, two or more coated regions and one, two or more uncoated regions, wherein the coated regions cover at least 60%, 70%, 80%, or 90% of the surfaces. Further, the uncoated region may be considered uncoated to the extent it does not have an electrically conductive coating - the uncoated region may have other types of surface coatings in certain embodiments.

[00216] In various embodiments, an ultrasound system includes a transducer with a transduction element (e.g., a flat, round, circular, cylindrical, annular, have rings, concave, convex, contoured or other shaped transduction element).

[00217] In various embodiments, an ultrasound transduction system, includes a transduction element (e.g., a cylindrical transduction element), and a power source

configured to drive the transduction element, wherein the transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth, wherein the transduction element comprises a first surface and a second surface, wherein the first surface comprises an electrically conductive coating, wherein the second surface comprises at least one electrically conductive coated region and at least one uncoated region that is not coated with an electrically conductive coating, wherein the at least one coated region on the second surface comprises a conductive material that forms an electrode when the power source is in electric communication with the at least one coated region, wherein the at least one coated region on the second surface is configured to reduce edge noise at the linear focal zone at the focal depth.

[00218] In various embodiments, an ultrasound transduction system includes a cylindrical transduction element and a power source configured to drive the cylindrical transduction element, wherein the cylindrical transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth. In some embodiments, the cylindrical transduction element comprises a first surface and a second surface, wherein the first surface comprises a coating, wherein the second surface comprises at least one coated region and at least one uncoated region, wherein the at least one coated region on the second surface comprises a conductive material that forms an electrode when the power source is in electric communication with the at least one coated region, wherein the at least one coated region on the second surface is configured to reduce edge noise at the linear focal zone at the focal depth.

[00219] In an embodiment, the uncoated region does not comprise a conductive material. In an embodiment, the conductive material is a metal (e.g., silver, gold, platinum, mercury, and/or copper, or an alloy). In an embodiment, the first surface is a concave surface and the second surface is a convex surface. In an embodiment, the first surface is a convex surface and the second surface is a concave surface. In an embodiment, the cylindrical transduction element is housed within an ultrasonic hand-held probe, wherein the ultrasonic probe includes a housing, the cylindrical transduction element, and a motion mechanism, wherein the ultrasound transducer is movable within the housing, wherein the motion mechanism is attached to the

ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing. In an embodiment, the motion mechanism automatically moves the cylindrical transduction element to heat a treatment area at the focal depth to a temperature in a range between 40 - 65°C (e.g., 40 - 45, 40- 50, 40- 55, 45 - 60, 45 - 55, 45 - 50°C, and any values therein). In an embodiment, the reduction of edge noise facilitates the production of a uniform (e.g., completely uniform, substantially uniform, about uniform) temperature in a treatment area. In an embodiment, the reduction of edge noise facilitates the efficient and consistent treatment of a tissue, wherein the cylindrical transduction element is configured to apply ultrasonic therapy to a treatment zone at the focal depth in the tissue. In an embodiment, the reduction of edge noise reduces a peak such that a variance around the focal depth is reduced by 75 - 200% (e.g., 75 - 100, 80 - 150, 100 - 150, 95 - 175%, and any values therein). In an embodiment, the reduction of edge noise reduces a peak such that a variance of intensity around the focal depth is 5 mm or less (e.g., 4.5, 4, 3.5, 3, 2.5, 2, 1.5, 1, 0.5 or less). In an embodiment, the reduction of edge noise reduces a variance in focal gain in a range of 0.01 - 10 (e.g., 1 - 5, 2 - 8, 0.5 - 3, and any values therein). In an embodiment, the power source is configured to drive the cylindrical transduction element to produce a temperature in a range of 42 - 55°C (e.g., 43 - 48, 45 - 53, 45 - 50°C, and any values therein) in a tissue at the focal depth. In an embodiment, a temperature sensor is located on the housing proximate an acoustic window in the housing configured to measure a temperature at a skin surface. In an embodiment, a system includes one or more imaging elements, wherein the cylindrical transduction element has an opening configured for placement of the one or more imaging elements. In an embodiment, the imaging element is configured to confirm a level of acoustic coupling between the system and a skin surface. In an embodiment, the imaging element is configured to confirm a level of acoustic coupling between the system and a skin surface via any one of the group consisting of: defocused imaging and Voltage Standing Wave Ratio (VSWR). In an embodiment, the imaging element is configured to measure a temperature at a target tissue at the focal depth below a skin surface. In an embodiment, the imaging element is configured to measure a temperature at a target tissue at the focal depth below a skin surface with any one of the group of Acoustic Radiation Force Impulse (ARFI), Shear Wave Elasticity Imaging (SWEI), and measurement of attenuation.

[00220] In several embodiments, a method of heating tissue with a cylindrical ultrasound transducer includes providing a cylindrical transduction element comprising a first surface, a second surface, a coated region, and an uncoated region. In some embodiments, the coated region comprises an electrical conductor. In some embodiments, the uncoated region does not comprise an electrical conductor. In some embodiments, the first surface comprises at least one coated region, wherein the second surface comprises the uncoated region and a plurality of coated regions, applying a current to the coated region, thereby directing ultrasound energy to a linear focal zone at a focal depth, wherein the ultrasound energy produces a reduction in focal gain at the linear focal zone.

[00221] In several embodiments, a cosmetic method of non-invasively and non-ablatively heating tissue with a heating source (e.g., a cylindrical ultrasound transducer) to heat the region under a subject's skin by between 5-25°C) while causing the temperature at the skin surface to stay the same or increases to a temperature that does not causing discomfort (e.g., by 1-5°C, 1-10°C, or 1-15°C). This differential aids in the comfort of the subject. The heating, in one embodiment, occurs in increments over a period of 5-120 mins with a graded or gradual increase in temperature. The heating can be performed by the cylindrical ultrasound transducer systems described herein. Optionally, an ablative or coagulative energy can subsequently be applied by increasing the temperature by another 5-25°C. The initial pre-heating step or bulk heating is advantageous because it allows less energy to be applied to achieve the coagulative/ablative state. In one embodiment, the initial pre-heating step is performed with a heating source other than an ultrasound transducer. For example, radiofrequency, microwave, light, convective, convers10n, and/or conductive heat sources can be used instead of or in addition to ultrasound.

[00222] In several embodiments, a non-invasive, cosmetic method of heating tissue includes applying a cosmetic heating system to a skin surface, wherein the cosmetic heating system comprises a hand-held probe. In some embodiments, the hand-held probe comprises a housing that encloses an ultrasound transducer configured to heat tissue below the skin surface to a tissue temperature in the range of 40 - 50°C (e.g., 44 - 47°C, 41 - 49°C, 45 - 50°C, and any values therein). In some

embodiments, the ultrasound transducer comprises a cylindrical transduction element comprising a first surface, a second surface, a coated region, and an uncoated region, wherein the coated region comprises an electrical conductor, wherein the first surface comprises at least one coated region, wherein the second surface comprises the uncoated region and a plurality of coated regions. In some embodiments, the method includes applying a current to the plurality of coated regions, thereby directing ultrasound energy to a linear focal zone at a focal depth, wherein the ultrasound energy produces a reduction in focal gain at the linear focal zone, thereby heating the tissue at the focal depth in the linear focal zone to the tissue temperature in the range of 40 - 50°C for a cosmetic treatment duration of less than 1 hour (e.g., 1 - 55, 10 - 30, 5 - 45, 15 - 35, 20 - 40 minutes and any values therein), thereby reducing a volume of an adipose tissue in the tissue.

[00223] In an embodiment, the reduction of focal gain facilitates the efficient and consistent treatment of tissue, wherein the cylindrical transduction element is configured to apply ultrasonic therapy to a thermal treatment zone at a focal depth. In an embodiment, the reduction of focal gain reduces a peak such that a variance around the focal depth is reduced by 25 - 100% (e.g., 30 - 50, 45 - 75, 50 - 90%, and any values therein). In an embodiment, the reduction of focal gain reduces a peak such that a variance of intensity around the focal depth is 5 mm or less (e.g., 1, 2, 3, 4 mm or less). In an embodiment, the reduction of focal gain reduces a variance in focal gain in a range of 0.01 - 10 (e.g., 0.06, 3, 4.5, 8, or any values therein). In an embodiment, the electrical conductor is a metal. In an embodiment, the first surface is a concave surface and the second surface is a convex surface. In an embodiment, the first surface is a convex surface and the second surface is a concave surface. In an embodiment, the cylindrical transduction element is housed within an ultrasonic handheld probe, wherein the ultrasonic probe includes a housing, the cylindrical transduction element, and a motion mechanism, wherein the ultrasound transducer is movable within the housing, wherein the motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing. In an embodiment, the motion mechanism automatically moves the cylindrical transduction element to heat a treatment area at the focal depth to a temperature in a range between 40 - 65 degrees Celsius. In an

embodiment, the cylindrical transduction element produces a temperature in a range of 42 - 55°C in a tissue at the focal depth. In an embodiment, the method also includes imaging tissue with one or more imaging elements, wherein the cylindrical transduction element has an opening configured for placement of the one or more imaging elements. In an embodiment, the method also includes confirming a level of acoustic coupling between the system and a skin surface with an image from the imaging element. In an embodiment, the method also includes confirming a level of acoustic coupling between the system and a skin surface with the imaging element using any one of the group consisting of: defocused imaging and Voltage Standing Wave Ratio (VSWR). In an embodiment, the method also includes measuring a temperature at a target tissue at the focal depth below a skin surface with the imaging element. In an embodiment, the method also includes measuring a temperature with the imaging element at a target tissue at the focal depth below a skin surface with any one of the group of Acoustic Radiation Force Impulse (ARFI), Shear Wave Elasticity Imaging (SWEI), and measurement of attenuation.

[00224] In various embodiments, systems and methods for ultrasound treatment of tissue are configured to provide cosmetic treatment. Various embodiments of the present invention address potential challenges posed by administration of ultrasound therapy. In various embodiments, the amount of time and/or energy to create a thermal treatment zone (also referred to herein "TTZ") for a desired cosmetic and/or therapeutic treatment for a desired clinical approach at a target tissue is reduced. In various embodiments, tissue below or at a skin surface such as epidermis, dermis, platysma, lymph node, nerve, fascia, muscle, fat, and/or superficial muscular aponeurotic system ("SMAS"), are treated non-invasively with ultrasound energy. In various embodiments, tissue below or at a skin surface such as epidermis, dermis, platysma, lymph node, nerve, fascia, muscle, fat, and/or SMAS are not treated. The ultrasound energy can be focused at one or more treatment zones, can be unfocused and/or defocused, and can be applied to a region of interest to achieve a cosmetic and/or therapeutic effect. In various embodiments, systems and/or methods provide non-invasive dermatological treatment to tissue through heating, thermal treatment, coagulation, ablation, and/or tissue tightening (including, for example, hyperthermia,

thermal dosimetry, apoptosis, and lysis). In one embodiment, dermal tissue volume is increased. In one embodiment, fat tissue volume is reduced, or decreased.

[00225] In various embodiments, target tissue is, but is not limited to, any of skin, eyelids, eye lash, eye brow, caruncula lacrimalis, crow's feet, wrinkles, eye, nose, mouth, tongue, teeth, gums, ears, brain, chest, back, buttocks, legs, arms, hands, arm pits, heart, lungs, ribs, abdomen, stomach, liver, kidneys, uterus, breast, vagina, penis, prostate, testicles, glands, thyroid glands, internal organs, hair, muscle, bone, ligaments, cartilage, fat, fat lobuli, adipose tissue, cellulite, subcutaneous tissue, implanted tissue, an implanted organ, lymphoid, a tumor, a cyst, an abscess, or a portion of a nerve, or any combination thereof. In several embodiments disclosed herein, non-invasive ultrasound is used to achieve one or more of the following effects: a face lift, a brow lift, a chin lift, an eye treatment, a wrinkle reduction, a scar reduction, a fat reduction, a reduction in the appearance of cellulite, a décolletage treatment, a burn treatment, a tattoo removal, a vein reduction, a treatment on a sweat gland, a treatment of hyperhidrosis, sun spot removal, an acne treatment, and a pimple removal. In some embodiments, two, three or more beneficial effects are achieved during the same treatment session, and may be achieved simultaneously.

[00226] Various embodiments of the present invention relate to devices or methods of controlling the delivery of energy to tissue. In various embodiments, various forms of energy can include acoustic, ultrasound, light, laser, radio-frequency (RF), microwave, electromagnetic, radiation, thermal, cryogenic, electron beam, photon-based, magnetic, magnetic resonance, and/or other energy forms. Various embodiments of the present invention relate to devices or methods of splitting an ultrasonic energy beam into multiple beams. In various embodiments, devices or methods can be used to alter the delivery of ultrasound acoustic energy in any procedures such as, but not limited to, therapeutic ultrasound, diagnostic ultrasound, non-destructive testing (NDT) using ultrasound, ultrasonic welding, any application that involves coupling mechanical waves to an object, and other procedures. Generally, with therapeutic ultrasound, a tissue effect is achieved by concentrating the acoustic energy using focusing techniques from the aperture. In some instances,

high intensity focused ultrasound (HIFU) is used for therapeutic purposes in this manner. In one embodiment, a tissue effect created by application of therapeutic ultrasound at a particular location (e.g., depth, width) to can be referred to as creation of a thermal treatment zone. It is through creation of thermal treatment zones at particular positions that thermal and/or mechanical heating, coagulation, and/or ablation of tissue can occur noninvasively or remotely offset from the skin surface.

[00227] System Overview

[00228] Various embodiments of ultrasound treatment and/or imaging devices are described in U.S. Publication No. US 2011/0112405, which is a national phase publication from International Publication WO 2009/149390, each of which is incorporated in its entirety by reference herein.

[00229] With reference to the illustration in FIG. 1, an embodiment of an ultrasound system 20 includes a hand wand 100, module 200, and a controller 300. The hand wand 100 can be coupled to the controller 300 by an interface 130, which may be a wired or wireless interface. The interface 130 can be coupled to the hand wand 100 by a connector 145. The distal end of the interface 130 can be connected to a controller connector on a circuit 345. In one embodiment, the interface 130 can transmit controllable power from the controller 300 to the hand wand 100. In various embodiments, the controller 300 can be configured for operation with the hand wand 100 and the module 200, as well as the overall ultrasound system 20 functionality. In various embodiments, a controller 300 is configured for operation with a hand wand 100 with one or more removable modules 200, 200', 200", etc. The controller 300 can include an interactive graphical display 310, which can include a touchscreen monitor and Graphic User Interface (GUI) that allows the user to interact with the ultrasound system 20. As is illustrated, the graphical display 315 includes a touchscreen interface 315. In various embodiments, the display 310 sets and displays the operating conditions, including equipment activation status, treatment parameters, system messages and prompts, and ultrasound images. In various embodiments, the controller 300 can be configured to include, for example, a microprocessor with software and input/output devices, systems and devices for controlling electronic

and/or mechanical scanning and/or multiplexing of transducers and/or multiplexing of transducer modules, a system for power delivery, systems for monitoring, systems for sensing the spatial position of the probe and/or transducers and/or multiplexing of transducer modules, and/or systems for handling user input and recording treatment results, among others. In various embodiments, the controller 300 can include a system processor and various analog and/or digital control logic, such as one or more of microcontrollers, microprocessors, field-programmable gate arrays, computer boards, and associated components, including firmware and control software, which may be capable of interfacing with user controls and interfacing circuits as well as input/output circuits and systems for communications, displays, interfacing, storage, documentation, and other useful functions. System software running on the system process may be configured to control all initialization, timing, level setting, monitoring, safety monitoring, and all other ultrasound system functions for accomplishing user-defined treatment objectives. Further, the controller 300 can include various input/output modules, such as switches, buttons, etc., that may also be suitably configured to control operation of the ultrasound system 20. In one embodiment, the controller 300 can include one or more data ports 390. In various embodiments, the data ports 390 can be a USB port, Bluetooth port, IrDA port, parallel port, serial port, and the like. The data ports 390 can be located on the front, side, and/or back of the controller 300, and can be used for accessing storage devices, printing devices, computing devices, etc. The ultrasound system 20 can include a lock 395. In one embodiment, in order to operate the ultrasound system 20, the lock 395 should be unlocked so that a power switch 393 may be activated. In one embodiment, the lock 395 can be connectable to the controller 300 via a data port 390 (e.g., a USB port). The lock 395 could be unlocked by inserting into the data port 390 an access key (e.g., USB access key), a hardware dongle, or the like. The controller 300 can include an emergency stop button 392, which can be readily accessible for emergency deactivation.

[00230] As is illustrated in FIG. 1, in one embodiment, the hand wand 100 includes one or more finger activated controllers or switches, such as 150 and 160. In one embodiment, the hand wand 100 can include a removable module 200. In other embodiments, the module 200 may be non-removable. The module 200 can be

mechanically coupled to the hand wand 100 using a latch or coupler 140. An interface guide 235 can be used for assisting the coupling of the module 200 to the hand wand 100. The module 200 can include one or more ultrasound transducers 280. In some embodiments, an ultrasound transducer 280 includes one or more ultrasound elements 281. The module 200 can include one or more ultrasound elements 281. The elements 281 can be therapy elements, and/or imaging elements. The hand wand 100 can include imaging-only modules 200, treatment-only modules 200, imaging-and-treatment modules 200, and the like. In one embodiment, the imaging is provided through the hand wand 100. In one embodiment, the control module 300 can be coupled to the hand wand 100 via the interface 130, and the graphic user interface 310 can be configured for controlling the module 200. In one embodiment, the control module 300 can provide power to the hand wand 100. In one embodiment, the hand wand 100 can include a power source. In one embodiment, the switch 150 can be configured for controlling a tissue imaging function and the switch 160 can be configured for controlling a tissue treatment function.

[00231] In one embodiment, the module 200 can be coupled to the hand wand 100. The module 200 can emit and receive energy, such as ultrasonic energy. The module 200 can be electronically coupled to the hand wand 100 and such coupling may include an interface which is in communication with the controller 300. In one embodiment, the interface guide 235 can be configured to provide electronic communication between the module 200 and the hand wand 100. The module 200 can comprise various probe and/or transducer configurations. For example, the module 200 can be configured for a combined dual-mode imaging/therapy transducer, coupled or co-housed imaging/therapy transducers, separate therapy and imaging probes, and the like. In one embodiment, when the module 200 is inserted into or connected to the hand wand 100, the controller 300 automatically detects it and updates the interactive graphical display 310.

[00232] In various embodiments, tissue below or even at a skin surface such as epidermis, dermis, hypodermis, fascia, and SMAS, and/or muscle are treated non-invasively with ultrasound energy. Tissue may also include blood vessels and/or

nerves. The ultrasound energy can be focused, unfocused or defocused and applied to a region of interest containing at least one of epidermis, dermis, hypodermis, fascia, and SMAS to achieve a therapeutic effect. FIG. 2 is a schematic illustration of the ultrasound system 20 coupled to a region of interest 10, such as with an acoustic gel. With reference to the illustration in FIG. 2, an embodiment of the ultrasound system 20 includes the hand wand 100, the module 200, and the controller 300. In various embodiments, tissue layers of the region of interest 10 can be at any part of the body of a subject. In various embodiments, the tissue layers are in the head, face, neck and/or body region of the subject. The cross-sectional portion of the tissue of the region of interest 10 includes a skin surface 501, an epidermal layer 502, a dermal layer 503, a fat layer 505, a SMAS 507, and a muscle layer 509. The tissue can also include the hypodermis 504, which can include any tissue below the dermal layer 503. The combination of these layers in total may be known as subcutaneous tissue 510. Also illustrated in FIG. 2 is a treatment zone 525 which is the active treatment area below the surface 501. In one embodiment, the surface 501 can be a surface of the skin of a subject 500. Although an embodiment directed to therapy at a tissue layer may be used herein as an example, the system can be applied to any tissue in the body. In various embodiments, the system and/or methods may be used on muscles (or other tissue) of the face, neck, head, arms, legs, or any other location in the body. In various embodiments, the therapy can be applied to a face, head, neck, submental region, shoulder, arm, back, chest, buttock, abdomen, stomach, waist, flank, leg, thigh, or any other location in or on the body.

[00233] Band Therapy Using A Cylindrical Transducer

[00234] In various embodiments, a transducer 280 can comprise one or more therapy elements 281 that can have various shapes that correspond to various focal zone geometries. In one embodiment, the transducer 280 comprises a single therapy element 281. In one embodiment, the transducer 280 does not have a plurality of elements. In one embodiment, the transducer 280 does not have an array of elements. In several embodiments, the transducers 280 and/or therapy elements 281 described herein can be flat, round, circular, cylindrical, annular, have rings, concave, convex, contoured, and/or have any shape. In some embodiments, the transducers

280 and/or therapy elements 281 described herein are not flat, round, circular, cylindrical, annular, have rings, concave, convex, and/or contoured. In one embodiment, the transducers 280 and/or therapy elements 281 have a mechanical focus. In one embodiment, the transducers 280 and/or therapy elements 281 do not have a mechanical focus. In one embodiment, the transducers 280 and/or therapy elements 281 have an electrical focus. In one embodiment, the transducers 280 and/or therapy elements 281 do not have an electrical focus. Although a cylinder transducer and/or a cylindrical element is discussed here, the transducer and/or element need not be cylindrical. In several embodiments, the transducer and/or element has one or more shapes or configurations that cause edge effects, such as variance, spikes or other inconsistencies in the delivery of ultrasound. For example, the transducer and/or element may have one or more non-linear (e.g., curved) portions. A transducer may be comprised of one or more individual transducers and/or elements in any combination of focused, planar, or unfocused single-element, multi-element, or array transducers, including 1-D, 2-D, and annular arrays; linear, curvilinear, sector, or spherical arrays; spherically, cylindrically, and/or electronically focused, defocused, and/or lensed sources. In one embodiment, the transducer is not a multi-element transducer. In one embodiment, a transducer 280 can include a spherically shaped bowl with a diameter and one or more concave surfaces (with respective radii or diameters) geometrically focused to a single point TTZ 550 at a focal depth 278 below a tissue surface, such as skin surface 501. In one embodiment, a transducer 280 may be radially symmetrical in three dimensions. For example, in one embodiment, transducer 280 may be a radially symmetrical bowl that is configured to produce a focus point in a single point in space. In some embodiments, the transducer is not spherically shaped. In some embodiments, the element is not spherically shaped.

[00235] In various embodiments, increasing the size (e.g. width, depth, area) and/or number of focus zone locations for an ultrasonic procedure can be advantageous because it permits treatment of a patient at varied tissue widths, heights and/or depths even if the focal depth 278 of a transducer 280 is fixed. This can provide synergistic results and maximizing the clinical results of a single treatment session. For example, treatment at larger treatment areas under a single

surface region permits a larger overall volume of tissue treatment, which can heat larger tissue volumes, and which can result in enhanced collagen formation and tightening. Additionally, larger treatment areas, such as at different depths, affects different types of tissue, thereby producing different clinical effects that together provide an enhanced overall cosmetic result. For example, superficial treatment may reduce the visibility of wrinkles and deeper treatment may induce skin tightening and/or collagen growth. Likewise, treatment at various locations at the same or different depths can improve a treatment. In various embodiments, a larger treatment area can be accomplished using a transducer with a larger focus zones (e.g., such as a linear focus zone compared to a point focus zone).

[00236] In one embodiment, as illustrated in FIGS. 3 and 4, a transducer 280 comprises a cylindrical transduction element 281. In FIG. 4, the view of the cylindrical transduction element 281, which has a concave surface 282 and a convex surface 283, is sectioned to show energy emission from the concave surface to a linear TTZ 550. The cylindrical transduction element 281 extends linearly along its longitudinal axis (X-axis, azimuth) with a curved cross section along a Y-axis (elevation). In one embodiment, the cylindrical surface has a radius at a focal depth (z-axis) at the center of the curvature of the cylindrical surface, such that the TTZ 550 is focused at the center of the radius. For example, in one embodiment, cylindrical transduction element 281 has a concave surface that extends like a cylinder that produces a focus zone that extends along a line, such as a therapy line, such as TTZ 550. The focus zone TTZ 550 extends along the width (along the X-axis, azimuth) of the cylindrical transduction element 281, in a line parallel to the longitudinal axis of the cylindrical transduction element 281. As illustrated in FIG. 3, the TTZ 550 is a line extending in and/or out of the page. In various embodiments of the cylindrical transduction element 281, a concave surface directs ultrasound energy to a linear TTZ 550. Cylindrical transduction element 281 need not be cylindrical; in some embodiments, element 281 is a transduction element having one or more curved or non-linear portions.

[00237] In various embodiments, transducers 280 can comprise one or more transduction elements 281. The transduction elements 281 can comprise a

piezoelectrically active material, such as lead zirconate titanate (PZT), or any other piezoelectrically active material, such as a piezoelectric ceramic, crystal, plastic, and/or composite materials, as well as lithium niobate, lead titanate, barium titanate, and/or lead metaniobate. In various embodiments, in addition to, or instead of, a piezoelectrically active material, transducers can comprise any other materials configured for generating radiation and/or acoustical energy. In one embodiment, when cylindrical transduction element 281 comprises a piezoelectric ceramic material that is excited by an electrical stimulus, the material may expand or contract. The amount of expansion or contraction is related to boundary conditions in the ceramic as well as the magnitude of the electric field created in the ceramic. In some embodiments of conventional HIFU design, the front surface (e.g. subject side) is coupled to water and the back surface of a transducer 280 is coupled to a low impedance medium which is typically air. In some embodiments, although the ceramic is free to expand at the back interface, essentially no mechanical energy is coupled from the ceramic to the air because of the significant acoustic impedance disparity. This results in this energy at the back of the ceramic reflecting and exiting the front (or subject side) surface. As illustrated in an embodiment in FIGS. 3 - 5B, the focus is created by forming, casting, and/or machining the ceramic to the correct radius-of-curvature. In one embodiment, a flat transducer material is bent to form a cylindrical transducer. In various embodiments, transducers 280 and/or therapy elements 281 can be configured to operate at different frequencies and treatment depths. Transducer properties can be defined by a focal length (FL), sometimes referred to as a focal depth 278. The focal depth 278 is the distance from the concave cylindrical surface to the focal zone TTZ 550. In various embodiments, the focal depth 278 is the sum of a standoff distance 270 and a treatment depth 279 when the housing of a probe is placed against a skin surface. In one embodiment, the standoff distance 270, or offset distance 270, is the distance between the transducer 280 and a surface of an acoustically transparent member 230 on the housing of a probe. The treatment depth 279 is a tissue depth 279 below a skin surface 501, to a target tissue. In one embodiment, the height of the aperture in the curved dimension is increased or maximized to have a direct effect on overall focal gain, which correlates to the ability to heat tissue. For example, in one embodiment, the height of the aperture in the curved dimension is maximized for a treatment depth

of 6 mm or less. In one embodiment, as the aperture is increased (e.g. decreasing the $f\#$), the actual heating zone gets closer to the surface.

[00238] In one embodiment, a transducer can be configured to have a focal depth 278 of 6 mm, 2 - 12 mm, 3 - 10 mm, 4 - 8 mm, 5 - 7 mm. In other embodiments, other suitable values of focal depth 278 can be used, such as focal depth 278 of less than about 15 mm, greater than about 15 mm, 5 - 25 mm, 10 - 20 mm, etc. Transducer modules can be configured to apply ultrasonic energy at different target tissue depths. In one embodiment, a therapy of 20 mm or less (e.g., 0.1 mm - 20 mm, 5 - 17 mm, 10 - 15 mm). In one embodiment, a device that goes to 6 mm or less has a radius of curvature (ROC) of 13.6 mm, with a ratio of treatment depth to ROC at approximately 44%. In one embodiment, the height of the element is 22 mm. In one embodiment, using an aspect ratio for a treatment depth of 20 mm, the aperture height would be 74.5 mm with a ROC of 45 mm.

[00239] As illustrated in FIGS. 5A-5B, 7, 9 and 10 in several embodiments, a system may comprise a movement mechanism 285 configured to move a transducer 280 comprising a cylindrical transduction element 281 in one, two, three or more directions. In one embodiment, a motion mechanism 285 can move in a linear direction, one or both ways, denoted by the arrow marked 290 in order move a TTZ 550 through tissue. In various embodiments, the motion mechanism 285 can move the transducer in one, two, and/or three linear dimensions and/or one, two, and/or three rotational dimensions. In one embodiment, a motion mechanism 285 can move in up to six degrees of freedom. Movement of the TTZ 550 can be with the transducer continuously delivering energy to create a treatment area 552. In one embodiment, a movement mechanism 285 can automatically move the cylindrical transduction element 281 across the surface of a treatment area so that the TTZ 550 can form a treatment area 552.

[00240] As indicated in FIGS. 6, 7, and 8, a cylindrical transduction element 281 can be connected to a motion mechanism 285 and placed inside a module 200 or a probe. In various embodiments, a movement mechanism 285, or a motion mechanism 285, moves the transducer 280 and/or treatment element 281 such that

the corresponding TTZ 550 moves to treat a larger treatment area 552. In various embodiments, a movement mechanism 285 is configured to move a transducer within a module or a probe. In one embodiment, a transducer is held by a transducer holder. In one embodiment, the transducer holder includes a sleeve which is moved along motion constraining bearings, such as linear bearings, namely, a bar (or shaft) to ensure a repeatable linear movement of the transducer. In one embodiment, sleeve is a spline bushing which prevents rotation about a spline shaft, but any guide to maintain the path of motion is appropriate. In one embodiment, the transducer holder is driven by a motion mechanism 285, which may be located in a hand wand or in a module, or in a probe. In one embodiment, a motion mechanism 285 includes any one or more of a scotch yoke, a movement member, and a magnetic coupling. In one embodiment, the magnetic coupling helps move the transducer. One benefit of a motion mechanism 285 is that it provides for a more efficient, accurate and precise use of an ultrasound transducer, for imaging and/or therapy purposes. One advantage this type of motion mechanism has over conventional fixed arrays of multiple transducers fixed in space in a housing is that the fixed arrays are a fixed distance apart. By placing transducer on a track (e.g., such as a linear track) under controller control, embodiments of the system and device provide for adaptability and flexibility in addition to efficiency, accuracy and precision. Real time and near real time adjustments can be made to imaging and treatment positioning along the controlled motion by the motion mechanism 285. In addition to the ability to select nearly any resolution based on the incremental adjustments made possible by the motion mechanism 285, adjustments can be made if imaging detects abnormalities or conditions meriting a change in treatment spacing and targeting. In one embodiment, one or more sensors may be included in the module. In one embodiment, one or more sensors may be included in the module to ensure that a mechanical coupling between the movement member and the transducer holder is indeed coupled. In one embodiment, an encoder may be positioned on top of the transducer holder and a sensor may be located in a portion of the module, or vice versa (swapped). In various embodiments the sensor is a magnetic sensor, such as a giant magnetoresistive effect (GMR) or Hall Effect sensor, and the encoder a magnet, collection of magnets, or multi-pole magnetic strip. The sensor may be positioned as a transducer module home position. In one embodiment, the sensor is

a contact pressure sensor. In one embodiment, the sensor is a contact pressure sensor on a surface of the device to sense the position of the device or the transducer on the patient. In various embodiments, the sensor can be used to map the position of the device or a component in the device in one, two, or three dimensions. In one embodiment the sensor is configured to sense the position, angle, tilt, orientation, placement, elevation, or other relationship between the device (or a component therein) and the patient. In one embodiment, the sensor comprises an optical sensor. In one embodiment, the sensor comprises a roller ball sensor. In one embodiment, the sensor is configured to map a position in one, two and/or three dimensions to compute a distance between areas or lines of treatment on the skin or tissue on a patient.

[00241] In various embodiments, a motion mechanism 285 can be any mechanism that may be found to be useful for movement of the transducer. In one embodiment, the motion mechanism 285 comprises a stepper motor. In one embodiment, the motion mechanism 285 comprises a worm gear. In various embodiments, the motion mechanism 285 is located in a module 200. In various embodiments, the motion mechanism 285 is located in the hand wand 100. In various embodiments, the motion mechanism 285 can provide for linear, rotational, multi-dimensional motion or actuation, and the motion can include any collection of points, lines and/or orientations in space. Various embodiments for motion can be used in accordance with several embodiments, including but not limited to rectilinear, circular, elliptical, arc-like, spiral, a collection of one or more points in space, or any other 1-D, 2-D, or 3-D positional and attitudinal motional embodiments. The speed of the motion mechanism 285 may be fixed or may be adjustably controlled by a user. One embodiment, a speed of the motion mechanism 285 for an image sequence may be different than that for a treatment sequence. In one embodiment, the speed of the motion mechanism 285 is controllable by a controller.

[00242] In some embodiments, the energy transmitted from the transducer is turned on and off, forming a non-continuous treatment area 552 such that the TTZ 550 moves with a treatment spacing between individual TTZ 550 positions. For example, treatment spacing can be about 1 mm, 1.5 mm, 2 mm, 5mm, 10 mm, etc. In

several embodiments, a probe can further comprise a movement mechanism configured to direct ultrasonic treatment in a sequence so that TTZs 550 are formed in linear or substantially linear sequences. For example, a transducer module can be configured to form TTZs 550 along a first linear sequence and a second linear sequence separated by treatment spacing between about 2 mm and 3 mm from the first linear sequence. In one embodiment, a user can manually move the transducer modules across the surface of a treatment area so that adjacent linear sequences of TTZs are created.

[00243] In one embodiment, a TTZ can be swept from a first position to a second position. In one embodiment, a TTZ can be swept from the first position to the second position repeatedly. In one embodiment, a TTZ can be swept from the first position, to the second position, and back to the first position. In one embodiment, a TTZ can be swept from the first position, to the second position, and back to the first position, and repeated. In one embodiment, multiple sequences of TTZs can be created in a treatment region. For example, TTZs can be formed along a first linear sequence and a second linear sequence separated by a treatment distance from the first linear sequence.

[00244] In one embodiment, TTZs can be created in a linear or substantially linear zone or sequence, with each individual TTZ separated from neighboring TTZs by a treatment spacing, such as shown in FIG. 9. FIG. 9 illustrates an embodiment of an ultrasound system 20 with a transducer 280 configured to treat tissue at a focal depth 278. In one embodiment, the focal depth 278 is a distance between the transducer 280 and the target tissue for treatment. In one embodiment, a focal depth 278 is fixed for a given transducer 280. In one embodiment, a focal depth 278 is variable for a given transducer 280. As illustrated in FIG. 9, in various embodiments, delivery of emitted energy 50 at a suitable focal depth 278, distribution, timing, and energy level is provided by the module 200 through controlled operation by the control system 300 to achieve the desired therapeutic effect of controlled thermal injury to treat at least one of the epidermis layer 502, dermis layer 503, fat layer 505, the SMAS layer 507, the muscle layer 509, and/or the hypodermis 504. FIG. 9 illustrates one embodiment of a depth that corresponds to a depth for treating

muscle. In various embodiments, the depth can correspond to any tissue, tissue layer, skin, epidermis, dermis, hypodermis, fat, SMAS, muscle, blood vessel, nerve, or other tissue. During operation, the module 200 and/or the transducer 280 can also be mechanically and/or electronically scanned along the surface 501 to treat an extended area. Before, during, and after the delivery of ultrasound energy 50 to at least one of the epidermis layer 502, dermis layer 503, hypodermis 504, fat layer 505, the SMAS layer 507 and/or the muscle layer 509, monitoring of the treatment area and surrounding structures can be provided to plan and assess the results and/or provide feedback to the controller 300 and the user via a graphical interface 310. In one embodiment, an ultrasound system 20 generates ultrasound energy which is directed to and focused below the surface 501. This controlled and focused ultrasound energy 50 creates the thermal treatment zone (TTZ) 550. In one embodiment, the TTZ 550 is a line. In one embodiment, the TTZ 550 is a point. In one embodiment, the TTZ 550 is a two dimensional region or plane. In one embodiment, the TTZ 550 is a volume. In one embodiment, the ultrasound energy 50 heat treats the subcutaneous tissue 510. In various embodiments, the emitted energy 50 targets the tissue below the surface 501 which heats, cuts, ablates, coagulates, micro-ablates, manipulates, and/or causes a lesion in the tissue portion 10 below the surface 501 at a specified focal depth 278. In one embodiment, during the treatment sequence, the transducer 280 moves in a direction denoted by the arrow marked 290 to move the TTZ 550.

[00245] In various embodiments, an active TTZ can be moved (continuously, or non-continuously) through tissue to form a treatment area 552, such as shown in FIG. 10. With reference to the illustration in FIG. 10, the module 200 can include a transducer 280 which can emit energy through an acoustically transparent member 230. In various embodiments, a depth may refer to the focal depth 278. In one embodiment, the transducer 280 can have an offset distance 270, which is the distance between the transducer 280 and a surface of the acoustically transparent member 230. In one embodiment, the focal depth 278 of a transducer 280 is a fixed distance from the transducer. In one embodiment, a transducer 280 may have a fixed offset distance 270 from the transducer to the acoustically transparent member 230. In one embodiment, an acoustically transparent member 230 is configured at a

position on the module 200 or the ultrasound system 20 for contacting the skin surface 501. In various embodiments, the focal depth 278 exceeds the offset distance 270 by an amount to correspond to treatment at a target area located at a tissue depth 279 below a skin surface 501. In various embodiments, when the ultrasound system 20 placed in physical contact with the skin surface 501, the tissue depth 279 is a distance between the acoustically transparent member 230 and the target area, measured as the distance from the portion of the hand wand 100 or module 200 surface that contacts skin (with or without an acoustic coupling gel, medium, etc.) and the depth in tissue from that skin surface contact point to the target area. In one embodiment, the focal depth 278 can correspond to the sum of an offset distance 270 (as measured to the surface of the acoustically transparent member 230 in contact with a coupling medium and/or skin 501) in addition to a tissue depth 279 under the skin surface 501 to the target region. In various embodiments, the acoustically transparent member 230 is not used.

[00246] In various embodiments, therapeutic treatment advantageously can be delivered at a faster rate and with improved accuracy by using a transducer configured to deliver energy to an expanded TTZ. This in turn can reduce treatment time and decrease pain experienced by a subject. In several embodiments, treatment time is reduced by creating a TTZ and sweeping the TTZ through an area or volume for treatment from a single transducer. In some embodiments, it is desirable to reduce treatment time and corresponding risk of pain and/or discomfort experienced by a patient. Therapy time can be reduced by treating larger areas in a given time by forming larger a TTZ 550, multiple TTZs simultaneously, nearly simultaneously, or sequentially, and/or moving the TTZ 550 to form larger treatment areas 552. In one embodiment, a reduction in treatment time is reduced by treating a given area or volume with multiple TTZs reduces the overall amount of movement for a device. In some embodiments, overall treatment time can be reduced 10%, 20%, 25%, 30%, 35%, 40%, 4%, 50%, 55%, 60%, 65%, 70%, 75%, 80% or more by through creation of continuous treatment areas 552 or discrete, segmented treatment areas 552 from a sequence of individual TTZs. In various embodiments, therapy time can be reduced by 10-25%, 30-50%, 40-80%, 50-90%, or approximately 40%, 50%, 60%, 70%, and/or 80%. Although treatment of a subject at different locations in one session may

be advantageous in some embodiments, sequential treatment over time may be beneficial in other embodiments. For example, a subject may be treated under the same surface region at one depth in time one, a second depth in time two, etc. In various embodiments, the time can be on the order of nanoseconds, microseconds, milliseconds, seconds, minutes, hours, days, weeks, months, or other time periods. For example, in some embodiments, the transducer module is configured to deliver energy with an on-time of 10 ms - 100 minutes (e.g., 100 ms, 1 second, 1 - 60 seconds, 1 minute - 10 minutes, 1 minute - 60 minutes, and any range therein). The new collagen produced by the first treatment may be more sensitive to subsequent treatments, which may be desired for some indications. Alternatively, multiple depth treatment under the same surface region in a single session may be advantageous because treatment at one depth may synergistically enhance or supplement treatment at another depth (due to, for example, enhanced blood flow, stimulation of growth factors, hormonal stimulation, etc.). In several embodiments, different transducer modules provide treatment at different depths. In one embodiment, a single transducer module can be adjusted or controlled for varied depths.

[00247] In one embodiment, an aesthetic treatment system includes an ultrasonic probe with a removable module that includes an ultrasound transducer configured to apply ultrasonic therapy to tissue at in a focal zone. In one embodiment, the focal zone is a point. In one embodiment, the focal zone is a line. In one embodiment, the focal zone is a two dimensional region or plane. In one embodiment, the focal zone is a volume. In various embodiments, a focal zone can be moved to sweep a volume between a first position and a second position. In various embodiments, one or more a focal zone locations are positioned in a substantially linear sequence within a cosmetic treatment zone. In one embodiment, a first set of locations is positioned within a first cosmetic treatment zone and a second set of locations is positioned within a second cosmetic treatment zone, the first zone being different from the second zone. In one embodiment, the first cosmetic treatment zone includes a substantially linear sequence of the first set of locations and the second cosmetic treatment zone includes a substantially linear sequence of the second set of locations.

[00248] In one embodiment, the transducer module 280 can provide an acoustic power in a range of about 1 W or less, between about 1 W to about 100 W, and more than about 100 W. In one embodiment, the transducer module 280 can provide an acoustic power at a frequency of about 1 MHz or less, between about 1 MHz to about 10 MHz, and more than about 10 MHz. In one embodiment, the module 200 has a focal depth 278 for a treatment at a tissue depth 279 of about 4.5 mm below the skin surface 501. Some non-limiting embodiments of transducers 280 or modules 200 can be configured for delivering ultrasonic energy at a tissue depth of 3 mm, 4.5 mm, 6 mm, less than 3 mm, between 3 mm and 4.5 mm, between 4.5 mm and 6 mm, more than more than 4.5 mm, more than 6 mm, etc., and anywhere in the ranges of 0.1 - 3 mm, 0.1 - 4.5 mm, 0.1 - 6 mm, 0.1 - 25 mm, 0.1 - 100 mm, etc. and any depths therein. In one embodiment, the ultrasound system 20 is provided with two or more removable transducer modules 280. In one embodiment, a transducer 280 can apply treatment at a tissue depth (e.g., about 6 mm). For example, a first transducer module can apply treatment at a first tissue depth (e.g., about 4.5 mm) and a second transducer module can apply treatment at a second tissue depth (e.g., of about 3 mm), and a third transducer module can apply treatment at a third tissue depth (e.g., of about 1.5 - 2 mm). In one embodiment, at least some or all transducer modules can be configured to apply treatment at substantially same depths. In various embodiments, the tissue depth can be 1.5 mm, 2 mm, 3 mm, 4.5 mm, 7 mm, 10 mm, 12 mm, 14 mm, 15 mm, 17 mm, 18 mm, and/or 20 mm, or any range therein (including but not limited to 12-20 mm, or higher).

[00249] In one embodiment, a transducer module permits a treatment sequence at a fixed depth at or below the skin surface. In one embodiment, a transducer module permits a treatment sequence at a range of depths below the skin surface. In several embodiments, the transducer module comprises a movement mechanism configured to move the ultrasonic treatment at the TTZ. In one embodiment, the linear sequence of individual TTZs has a treatment spacing in a range from about 0.01 mm to about 25 mm. For example, the spacing can be 1.1 mm or less, 1.5 mm or more, between about 1.1 mm and about 1.5 mm, etc. In one embodiment, the individual TTZs are discrete. In one embodiment, the individual TTZs are overlapping. In one embodiment, the movement mechanism is configured to be

programmed to provide variable spacing between the individual TTZs. In several embodiments, a transducer module comprises a movement mechanism configured to direct ultrasonic treatment in a sequence so that TTZs are formed in linear or substantially linear sequences separated by a treatment distance. For example, a transducer module can be configured to form TTZs along a first linear sequence and a second linear sequence separated by a treatment distance from the first linear sequence. In one embodiment, treatment distance between adjacent linear sequences of individual TTZs is in a range from about 0.01 mm to about 25 mm. For example, the treatment distance can be 2 mm or less, 3 mm or more, between about 2 mm and about 3 mm, etc. In several embodiments, a transducer module can comprise one or more movement mechanisms configured to direct ultrasonic treatment in a sequence so that TTZs are formed in linear or substantially linear sequences of individual thermal lesions separated by a treatment distance from other linear sequences. In one embodiment, the treatment distance separating linear or substantially linear TTZs sequences is the same or substantially the same. In one embodiment, the treatment distance separating linear or substantially linear TTZs sequences is different or substantially different for various adjacent pairs of linear TTZs sequences.

[00250] Band Therapy Using A Cylindrical Transducer with An Imaging Element

[00251] In various embodiments, including an imaging transducer or imaging element with a cylindrical transduction element 281 can be used to improve safety and/or efficacy of a treatment. In one embodiment, an imaging element can be used to confirm acceptable coupling between the ultrasound therapy transducer and/or identify target tissue below the skin surface. As illustrated at FIGS. 21 and 22, in various embodiments, a transducer 280 comprises a cylindrical transduction element 281 and one or more imaging elements 284. The imaging element 284 is configured to image a region of interest at any suitable tissue depths 279. In one embodiment, an imaging element is centered on a therapy element. In one embodiment, an imaging element is axis symmetric with a therapy element. In one embodiment, an imaging element is not axis symmetric with a therapy element. In one embodiment, the imaging axis may be pointed in a completely different direction and translated

from the therapy beam axis. In one embodiment, the number of imaging elements in the aperture may be greater than one. For example, in one embodiment, the imaging elements may be located on each corner of a cylinder pointed straight ahead and/or in the middle. In one embodiment, a combined imaging and cylindrical therapy transducer 280 comprises a cylindrical transduction element 281 and one or more imaging elements 284. In one embodiment, a combined imaging and cylindrical therapy transducer 280 comprises a cylindrical transduction element 281 with an opening 285 through which one imaging element 284 is configured to operate. In one embodiment, the opening 284 is a circular hole through the wall thickness of the cylindrical transduction element 281 at the center of the X-axis (azimuth) and Y-axis (elevation) of the cylindrical transduction element 281. In one embodiment, the imaging element 284 is circular in cross-section and fits in the opening 284.

[00252] In one embodiment, first and second removable transducer modules are provided. In one embodiment, each of the first and second transducer modules are configured for both ultrasonic imaging and ultrasonic treatment. In one embodiment, a transducer module is configured for treatment only. In one embodiment, an imaging transducer may be attached to a handle of a probe or a hand wand. The first and second transducer modules are configured for interchangeable coupling to a hand wand. The first transducer module is configured to apply ultrasonic therapy to a first treatment area, while the second transducer module is configured to apply ultrasonic therapy to a second treatment area. The second treatment area can be at a different depth, width, height, position, and/or orientation than the first treatment area.

[00253] Band Therapy Using A Coated Transducer Configured to Reduce Edge Effects

[00254] In various embodiments, treatment advantageously can be delivered with improved accuracy. Further, efficiency, comfort and safety can be increased if variance is reduced in a treatment area. This in turn can reduce treatment time and decrease pain experienced by a subject. In some instances, non-uniform heating at a focal zone can result from geometric aspects of a transducer. Inconsistencies in

pressure or temperature profiles can be attributed to edge effects, which can cause spikes in pressure or temperature around the focal zone of a transducer. Thus, with edge effects, instead of achieving a uniform line segment of heating, the segment is broken into many isolated hot spots which may fail to meet an objective a more uniform heat distribution at the focal zone. This phenomenon is further exacerbated at high heating rates which relate to elevated acoustic pressures. This is due to the generation of nonlinear harmonics created especially in areas of high pressure. Energy at harmonic frequencies is more readily absorbed than energy at the fundamental frequency. In one embodiment, energy absorption is governed by the following equation:

$$H = 2 \cdot \alpha \cdot f \cdot p^2 / Z \quad (1)$$

[00255] where alpha is the absorption constant in nepers per MHz cm, f is frequency in MHz, p is the pressure at that frequency, Z is the acoustic impedance of tissue, and H is the heating rate in Watt/cm³. In one embodiment, the amount of harmonics produced is proportional to the intensity. FIG. 23 shows the normalized harmonic pressure at the focal depth across an azimuth of one embodiment of a cylindrical element with an imaging element. FIG. 23 shows the rapid swings in harmonic pressure at this depth which causes hot spots and non-uniform heating.

[00256] In one embodiment, a way to combat these hot and cold spots that are the result from edge effects is to reduce the average intensity at the focal depth and/or increase the heating time. These two processes can reduce the amount on nonlinear heating as well as allow for the conduction of the heat away from the hot spot into the cold areas. The thermal conduction of tissue effectively acts as a low pass filter to the acoustic intensity distribution as the heating time increases. Although these methods may reduce the non-uniform heating issues, they can also reduce the localization of the heating zone and can also increase the treatment time. Therefore, three performance areas of ultrasound therapy, e.g. efficacy, comfort, and treatment time, are adversely affected. In one embodiment, a more normalized pressure profile results in more consistent therapy, such that temperature increase through heating, coagulation, and/or ablation is more predictable and can better

ensure the desired or targeted temperature profiles are obtained in the TTZ 550. In various embodiments, apodization of edge effects is accomplished with transducers coated in specific regions.

[00257] In one embodiment, use of coatings, or shadings, can help circumventing these issues such that efficacy, comfort and treatment time are optimized. FIG. 24 shows a harmonic pressure distribution from an embodiment of a shaded aperture, or a coated element, that has an imaging transducer. In one embodiment, the coated element is a coated cylindrical element with an imaging element. The variation in harmonic pressure across the treatment line varies by less than 1.5 dB with the highest intensity near the center and sharp edges at -10 mm and + 10 mm. In one embodiment, the coated element design does not require the conduction of heat away from hot spots since the tissue along the focused line has a uniform temperature increase during the absorption. Therefore, the amount of intensity at the focus can be increased to localize the heating zone and reduce treatment time.

[00258] In one embodiment, the coated element is a shaded therapeutic cylinder. In one embodiment, a coated element also has benefits outside the intended heating zone. In one embodiment, the boundary between the heated and unheated junction is vastly improved when compared to an uncoated element. FIG. 25 shows a comparison of harmonic pressure across an azimuth of an embodiment of a cylindrical element 280 compared to an embodiment of a coated cylindrical element 600 at this boundary. FIG. 25 shows that, in one embodiment, the possible harmonic pressures are approximately 20 dB lower for the shaded aperture with a coated cylindrical element 600, which helps confine the heating zone and maximize comfort. In one embodiment, areas of plating or non-plating are initially used to define regions where the piezoelectric material will be poled or not poled. Regions where there is plating define regions that will be poled or actually mechanically vibrating. In one embodiment, a cylindrical element 280 can be uncoated. Further, an uncoated region may be considered uncoated to the extent it does not have an electrically conductive coating - the uncoated region may have other types of surface coatings in certain embodiments. In one embodiment, a cylindrical element is

completely coated. For example, in one embodiment, a first transducer 280 includes a first coated region 287 that fully plates the concave surface 282 of the cylindrical transduction element and a second coated region 287 that fully plates the convex surface 283 of the cylindrical transduction element. A second coated transducer 600 includes a first coated region 287 that fully plates the concave surface 282 of the cylindrical transduction element and at least a second coated region 287 that partially plates the convex surface 283 of the cylindrical transduction element. As shown in FIG. 27, the fully coated first transducer 281 demonstrates the spikes in focal gain due to edge effects.

[00259] Referring to FIGS. 11A-13B, in one embodiment, transducer treatment profiles were plotted based on theoretical and experimental performance with a cylindrical transduction element 281 that was coated on the entire concave surface 282 and the entire convex surface 283 with a coating. In one embodiment, the coating is a metal. In one embodiment, the coating is a conductive metal. In one embodiment, the coating is an electrical conductor. In various embodiments, the coating is plated with any one or more of silver, gold, platinum, mercury, copper or other materials. In one embodiment, a coating comprises fired silver. In one embodiment, a surface is fully coated. In one embodiment, a surface is fully non-coated. In one embodiment, a surface is partially coated and partially non-coated. The normalized pressure is proportional to a thermal heating measure at the specified depth. The discontinuous spikes (pointed regions at the top of the plots) indicate pressure and/or temperature peaks that occur as a result of the geometric edge effects of the geometry of the cylindrical transduction element 281. In various embodiments, the spikes, or peaks, can be reduced with a coated transducer 600 comprising one or more coated regions 287. In one embodiment, the coated region 287 only partially coats a transducer surface. In one embodiment, the coated region 287 does not completely coat a transducer surface.

[00260] As shown in FIG. 26, in various embodiments, a coated transducer 600 comprises a cylindrical transduction element 281 with one or more coated regions 287. In various embodiments, the coated region 287 coats part, a portion, and/or all of a surface of the transducer 600. In various embodiments, the coated region 287

coats part or all of a surface of the cylindrical transduction element 281. In various embodiments, a coated transducer 600 comprises one or more imaging elements 284. In some embodiments, one, two, three or more imaging element(s) are placed in 'unused regions' of coatings/shading for the purpose of imaging.

[00261] The edge effects from the geometry of one embodiment of a combined imaging and cylindrical therapy transducer comprising a cylindrical transduction element 281 with an opening 285 through it are more pronounced due to the additional edges of the opening 285. FIG. 27 is a plot illustrating focal gain across the azimuth of two embodiments of combined imaging and cylindrical therapy transducers with different coatings. A first transducer 280 includes a first coated region 287 that fully plates the concave surface 282 of the cylindrical transduction element and a second coated region 287 that fully plates the convex surface 283 of the cylindrical transduction element. Both the first and the second coated regions 287 of the first transducer 280 are plated with silver. A second coated transducer 600 includes a first coated region 287 that fully plates the concave surface 282 of the cylindrical transduction element and at least a second coated region 287 that partially plates the convex surface 283 of the cylindrical transduction element. Both the first and the second coated regions 287 of the second transducer 600 are plated with silver. As shown in FIG. 27, the fully coated first transducer 281 demonstrates the spikes in focal gain due to edge effects. The partially coated second transducer 600 has a more consistent, normalized performance output with the spikes substantially reduced and/or removed. In various embodiments, a coated transducer 600 reduces the peaks such that variance around the focal depth is reduced by 1 - 50%, 25 - 100%, 75 - 200%, and/or 10 - 20%, 20 - 40% and 60 - 80%. In various embodiments, a coated transducer 600 reduces the peaks such that variance of the intensity in a location around the focal depth is $\pm 0.01 - 5$ mm, 5 mm or less, 4 mm or less, 3 mm or less, 2 mm or less, 1 mm or less, 0.5 mm or less, 0.25 mm or less, 0.1 mm or less, 0.05 mm or less, or any range therein. In various embodiments, a coated transducer 600 reduces the peaks in focal gain such that variance in focal gain is 0.01 - 0.1, 0.01 - 1.0, 0.01 - 5, 0.01 - 10, 1 - 10, 1 - 5, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or less, or any range therein.

[00262] As described in Example 4 below, FIGS. 28, 29, and 30 illustrate the embodiment of the performance of the partially coated second transducer 600 in FIG. 27 at different depths. In the illustrated embodiment, the partially coated second transducer 600 has a focal depth of 15 mm. In various embodiments, the focal depth can be at any depth. In various embodiments, the focal depth is at 7, 8, 9, 10, 12, 13, 13.6, 14, 15, 16, 17, 18, or any depth therein.

[00263] In one embodiment, the coated region 287 is plating. In one embodiment, the coated region 287 is a conductive material. In one embodiment, the coated region 287 is a semi-conductive material. In one embodiment, the coated region 287 is an insulator material. In various embodiments, the coated region 287 is silver, copper, gold, platinum, nickel, chrome, and/or any conductive material that will adhere with the surface of a piezoelectric material, or any combinations thereof. In one embodiment, the coated region 287 is silver plating.

[00264] In various embodiments, a cylindrical transduction element 281 has an azimuth (x-axis) dimension in the range of 1 - 50 mm, 5 - 40 mm, 10 - 20 mm, 15 - 25 mm, and/or 15 mm, 16 mm, 17 mm, 18 mm, 19 mm, 20 mm, 21 mm, 22 mm, 23 mm, 24 mm, and 25 mm. In various embodiments, a cylindrical transduction element 281 has an elevation (y-axis) dimension in the range of 1 - 50 mm, 5 - 40 mm, 10 - 20 mm, 15 - 25 mm, and/or 15 mm, 16 mm, 17 mm, 18 mm, 19 mm, 20 mm, 21 mm, 22 mm, 23 mm, 24 mm, and 25 mm. In various embodiments, a cylindrical transduction element 281 has focal depth (z-axis) dimension in the range of 1 - 50 mm, 5 - 40 mm, 10 - 20 mm, 15 - 25 mm, 12 - 17 mm, 13 - 15 mm, and/or 10 mm, 11 mm, 12 mm, 13 mm, 13.6 mm, 14 mm, 15 mm, 16 mm, 17 mm, 18 mm, 19 mm, 20 mm, 21 mm, 22 mm, 23 mm, 24 mm, and 25 mm. In some non-limiting embodiments transducers can be configured for a treatment zone at a tissue depth below a skin surface of 1.5 mm, 3 mm, 4.5 mm, 6 mm, less than 3 mm, between 1.5 mm and 3 mm, between 1.5 mm and 4.5 mm, more than more than 4.5 mm, more than 6 mm, and anywhere in the ranges of 0.1 mm - 3 mm, 0.1 mm - 4.5 mm, 3 mm - 7 mm, 3 mm - 9 mm, 0.1 mm - 25 mm, 0.1 mm - 100 mm, and any depths therein.

[00265] In various embodiments, a coated transducer 600 comprising a cylindrical transduction element 281 has one, two, three, four, or more coated regions 287. In one embodiment, a coated region 287 covers an entire surface of the element. In one embodiment, a coated region 287 covers a portion of a surface of the element. In various embodiments, the coated region 287 includes a conductive plating. In one embodiment, a coated region 287 includes a silver plating to form an electrode. When an electrical signal is applied to an electrode at a coated region 287, the coated region 287 expands and/or contracts the corresponding portion of the cylindrical transduction element 281. In various embodiments, the coated region 287 has a shape or border that is a complete or a partial point, edge, line, curve, radius, circle, oval, ellipse, parabola, star, triangle, square, rectangle, pentagon, polygon, a combination of shapes, or other shape. In various embodiments, a coated transducer 600 can also comprise an opening 285.

[00266] In one embodiment illustrated at FIG. 31, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two, three, four, or more coated regions 287 of one or more shapes on a convex 283 surface. In one embodiment, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two, three, four, or more coated regions 287 of one or more shapes on a concave 282 surface. In various embodiments, the coated region 287 has a lateral edge 293, a side edge 290, and a medial edge 291. The various edges can be straight, curved, and/or have a radius, and the sizes can be modified to result in various performance profiles.

[00267] In one embodiment illustrated at FIG. 32, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two, three, four, or more circular, round, curved and/or elliptical coated regions 287. In various embodiments, the coated region 287 has a lateral edge 293, a side edge 290, and a medial edge 291. The various edges can be straight, curved, and/or have a radius, and the sizes can be modified to result in various performance profiles.

[00268] In one embodiment illustrated at FIG. 33, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two, three, four, or

more triangular coated regions 287. In various embodiments, the coated region 287 has a lateral edge 293, a side edge 290, and a medial edge 291. The various edges can be straight, curved, and/or have a radius, and the sizes can be modified to result in various performance profiles.

[00269] In one embodiment illustrated at FIG. 34, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two or more square, rectangular, and/or polygon coated regions 287. In various embodiments, the coated region 287 has a lateral edge 293, a side edge 290, and a medial edge 291. The various edges and/or sizes can be modified to result in various performance profiles.

[00270] In one embodiment illustrated at FIG. 35, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two or more combined and/or mixed shape coated regions 287. In one embodiment illustrated at FIG. 35, a partially coated transducer 600 is a combined imaging and cylindrical therapy transducer comprising a cylindrical transduction element 281 with an opening 285 for an imaging element 284. In one embodiment, the coated transducer 600 includes a concave surface 282 that is fully plated with fired silver, and has a convex surface 283 with two coated regions 287 that are plated with fired silver to form electrodes. When an electrical signal is applied to an electrode at a coated region 287, the coated region 287 expands and/or contracts the corresponding portion of the cylindrical transduction element 281. In some embodiments, the shape may be applied before or after the poling process, as vibration will occur where the electrode is located. In various embodiments, an electrode could be defined before or after poling. In various embodiments, a coating pattern may be on the concave or convex surface. In one embodiment, the coated region 287 has a lateral edge 293, a first and second side edge 290, and a medial edge 291 with a central edge 297. The various edges can be straight, curved, and/or have a radius. Various dimensions 294, 295, 296, and the various edges can be modified to result in various performance profiles. In one embodiment, the medial edge 291 along the curved dimension (elevation) is a portion of an ellipse. In one embodiment, the medial edge 291 along the curved dimension (elevation) is a portion of a parabola. In one embodiment, the first and second side edge 290 along the uncurved dimension (azimuth) is a portion of a

parabola. In one embodiment, the first and second side edge 290 along the uncurved dimension (azimuth) is a portion of an ellipse.

[00271] In one embodiment illustrated at FIG. 36, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two, three, four, or more diamond, rhombus, and/or other polygon coated regions 287. In various embodiments, the coated region 287 has a lateral edge 293, a side edge 290, and a medial edge 291. The various edges and/or sizes can be modified to result in various performance profiles.

[00272] In one embodiment illustrated at FIGS. 37 and 38, a partially coated transducer 600 comprising a cylindrical transduction element 281 has one, two, three, four or more coated regions 287. In various embodiments, the coated region 287 has a lateral edge 293, a side edge 290, and a medial edge 291. In some embodiments, the coated region 287 is configured to position one, two, three, four, or more (e.g., multiple) thermal treatment zones through poling, phasic poling, biphasic poling, and/or multi-phasic poling. Various embodiments of ultrasound treatment and/or imaging devices with of multiple treatment zones enabled through poling, phasic poling, biphasic poling, and/or multi-phasic poling are described in U.S. Application No. 14/193,234 filed on February 28, 2014, which is incorporated in its entirety by reference herein.

[00273] Non-Therapeutic Uses of a Coated Cylindrical Transducer With Reduced Edge Effects

[00274] In various embodiments, a coated cylindrical transducer 600 comprising one or more coated regions 287 are configured for non-therapeutic use.

[00275] In one embodiment, a coated cylindrical transducer 600 comprising one or more coated regions 287 are configured for materials processing. In one embodiment, a coated cylindrical transducer 600 comprising one or more coated regions 287 is configured for ultrasonic impact treatment for the enhancement of

properties of a material, such as a metal, compound, polymer, adhesive, liquid, slurry, industrial material.

[00276] In one embodiment, a coated cylindrical transducer 600 comprising one or more coated regions 287 are configured for material heating. In various embodiments, the cylindrical transducer 600 is configured for cooking, heating, and/or warming materials, food, adhesives or other products.

[00277] Heating Tissue and Quantification of Thermal Dose for Ultrasound Band Therapy

[00278] As described above, in various embodiments, systems and/or methods provide non-invasive dermatological treatment to tissue through heating, hyperthermia, thermal dosimetry, thermal treatment, coagulation, ablation, apoptosis, lysis, increasing tissue volume, decreasing or reducing tissue volume, and/or tissue tightening. In one embodiment, dermal tissue volume is increased. In one embodiment, fat tissue volume is reduced, or decreased.

[00279] In various embodiments, band treatment involves metrics that quantify the magnitude of adipocyte death with heat. For example, in one embodiment, thermal dosage in a heat treatment relates time-temperature curves back to a single reference temperature, e.g. $T=43^{\circ}\text{C}$, using the Arrhenius equation. In one embodiment, a band treatment is configured under a relationship that that for every 1°C increase in tissue temperature above in a range above body temperature, the rate of cell death doubles. A theoretical survival fraction can then be determined by comparing the thermal dose to empirical data from the literature.

[00280] In various embodiments, band treatment provides improved thermal heating and treatment of tissue compared to diathermy or general bulk heating techniques. In general, normal body temperatures tend to range between about $33 - 37^{\circ}\text{C}$. In various embodiments, as tissue is heated in a range of about $37 - 43^{\circ}\text{C}$, physiological hyperthermia can take place, and exposure to this temperature range on order of, for example, a few hours, can result in increased normal tissue

metabolism and/or increased normal tissue blood flow, and in some embodiments, accelerated normal tissue repair. As temperature in the tissues reaches the higher ~ 43°C range and/or the tissue is subject to the temperature for longer periods of time (e.g., 2 hours, 3, hours or more) the tissue can experience acute tissue metabolism and/or acute tissue blood flow, and in some embodiments, accelerated normal tissue repair. In one embodiment, heating (e.g., bulk heating) of tissue to a range of about 42 - 55°C is performed. In various embodiments, heating of tissue to about 43 - 50°C can be considered adjuvant synergistic hyperthermia, and exposure to this temperature range on order of, for example, a few minutes, can result in immediate or delayed cell death, apoptosis, decreased tumor metabolism, increased tissue oxygen levels, increased tissue damage, increased sensitivity to therapy, vascular status, DNA damage, cell reproductive failure, and/or cell destruction. In various embodiments, heating of tissue to about 50 - 100°C can be considered surgical hyperthermia, and exposure to this temperature range on order of, for example, a few seconds or fractions of a second, can result in coagulation, ablation, vaporization, and immediate cell destruction.

[00281] In some embodiments of the invention, the temperature of the tissue treatment site (e.g., the adipocytes) is elevated to 38 - 43°C, and according to one embodiment, thereby increasing tissue metabolism and perfusion and accelerating tissue repair mechanisms. In other embodiments, the temperature of the tissue treatment site (e.g., the adipocytes) is elevated to 43 - 50°C, which in one embodiment can increase cell damage starts and result in immediate cell death, particularly when the temperature remains elevated on the order of several minutes to an hour (or longer). In yet other embodiments, the temperature of the tissue treatment site (e.g., the adipocytes) is elevated to above 50°C, which in one embodiment results in protein coagulation on the order of seconds and less and can lead to immediate cell death and ablation. In various embodiments, the temperature of the tissue treatment site is heated to 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 70, 75, 80, 90, or 100°C, and/or any range therein. In various embodiments, a treatment area has uniform temperature, a variance of 1%, 2%, 3%, 4%, 5%, 6%, 7 %, 8%, 9%, 10%, 12%, 15%,

20%, 25%, 30%, 40%, 50% or more. In various embodiments, a treatment area has a variance of +/- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 25°C or more.

[00282] In several embodiments, the invention comprises elevating the temperature of the tissue treatment site (e.g., the adipocytes) is elevated to 38 - 50°C for a time period between 1 - 120 minutes, and then optionally increasing the temperature in one, two, three, four five or more increments by 10-50%. As an example using three increments, the target temperatures may be increased as follows: (i) elevate temperature to about 40-42°C for 10-30 minutes, (ii) then optionally increase temperature by about 20% to elevate temperature to about 48-51°C for 1-10 minutes, and (iii) then optionally increase by about 10-50% for a shorter time frame. As another example, the target temperature may be increased as follows: (i) elevate temperature to about 50°C for 30 seconds to 5 minutes (e.g., about 1 minute) to destroy over 90%, 95% or 99% of target (e.g., adipose) cells, with an optional pre-heating step of raising the temperature to 38 - 49°C for a period of 10-120 minutes prior to the elevation to 50°C. As yet another example, in some embodiments, a non-invasive, cosmetic method of heating tissue, comprises applying a cosmetic heating system to a skin surface, wherein the cosmetic heating system comprises a hand-held probe, wherein the hand-held probe comprises a housing that encloses an ultrasound transducer configured to heat tissue below the skin surface to a tissue temperature in the range of 40 - 50°C, wherein the ultrasound transducer comprises a cylindrical transduction element comprising a first surface, a second surface, a coated region, and an uncoated region, wherein the coated region comprises an electrical conductor, wherein the first surface comprises at least one coated region, wherein the second surface comprises the uncoated region and a plurality of coated regions, applying a current to the plurality of coated regions, thereby directing ultrasound energy to a linear focal zone at a focal depth, wherein the ultrasound energy produces a reduction in focal gain at the linear focal zone, thereby heating the tissue at the focal depth in the linear focal zone to the tissue temperature in the range of 40 - 50°C for a cosmetic treatment duration of less than 1 hour, thereby reducing a volume of an adipose tissue in the tissue.

[00283] In one embodiment, a band therapy system uses a relationship between cell death and time-temperature dosages as quantified using the Arrhenius equation. The Arrhenius equation shows an exponential relationship exists between cell death and exposure time and temperature. Above a certain break temperature, the increase in the rate of cell killing with temperature is relatively constant. Time-temperature relationships to achieve isoeffective dose in several types of tissue appears to be conserved both in vitro and in-vivo across multiple cell types.

[00284] In some embodiments, clinical situations involve ramp-up of temperatures, cooling, and fluctuations when approaching and maintaining a steady state temperature. In various embodiments, different thermal profiles can produce the same thermal dose. In order to estimate the thermal dosage from a time-varying thermal profile, a temperature curve is discretized into small time steps, and the average temperature during each time step is calculated. The thermal dosage is then calculated as an equivalent exposure time at the break temperature (43°C) by integrating these temperatures according to equation (2):

$$t_{43} = \sum_{t=0}^{t=final} R^{(43-\bar{T})} \Delta t$$

$$t_{43} : \text{Equivalent time at } 43^{\circ}\text{C}$$

$$\bar{T} : \text{Average temperature during } \Delta t$$

$$R = \begin{cases} 0.5, T \geq 43^{\circ}\text{C} \\ 0.25, T < 43^{\circ}\text{C} \end{cases}$$

(2)

[00285] Equation (2) suggests that the increase in the rate of killing with temperature is relatively constant. In some embodiments, a 1 degree Celsius increase above a break point results in the rate of cell death doubles. FIGs. 39 and 40 illustrate theoretical cell death fractions over time depending on tissue temperature, with higher theoretical cell killing fractions at higher temperatures and/or higher periods of time. The higher a kill fraction (such as shown with kill fractions of 99%, 80%, 50%, 40%, and 20%) the higher a temperature and/or a time is used in an embodiment of a treatment.

[00286] Once a thermal dose has been calculated, a dose survival response can be estimated from empirical data. In one embodiment, an isoeffective dose of 43°C for 100 minutes theoretically yields a cell survival fraction of 1%. Based on the Arrhenius relationship, a similar surviving fraction can be obtained with an isoeffective dose of 44°C for 50 minutes, or 25 minutes at 45°C, etc. as tabulated in the table listing isoeffective dosages to theoretically achieve 1% survival fraction at FIG. 41, according to embodiments of the present invention.

[00287] In various embodiment, simulations of various embodiments of band therapy using a cylindrical transducer source conditions linked to the relationship between tissue and heat equation showed that successive treatment pulses obey linear superposition, which allows for simplification of the heat transfer physics so that the heating rate may be described as a temperature rise per time (degrees Celsius/sec), and as a temperature rise per pass (degrees Celsius/button push).

[00288] Heating Tissue via Ultrasound Band Therapy

[00289] In various embodiments, a band therapy system is configured for treating the tissue. For example, in one embodiment, a band treatment is configured for treatment of supraplatysmal submental fat. In one embodiment, a treatment of fat includes selectively causing thermal heat shock followed by apoptosis to a fat layer, at a depth of about 2.5 - 6.0 mm, without causing any major skin surface effects. In one embodiment, the treatment involves exposing fat to a bulk heating treatment with a temperature of 42-55°C for 1-5 minutes without exceeding 41°C on the skin surface, with physiologic/biologic effect (e.g. one or more of coagulation, apoptosis, fat cell lysis, etc.). In various embodiments, treatment with a band transducer treats tissue with isoeffective doses, as shown in a graph representing various levels of theoretical cell kill fractions in FIG. 42.

[00290] In various embodiments, a theoretical review of the effect of stacking multiple treatment pulses using the Khokhlov-Zabolotskaya-Kuznetsov (KZK) Equation was implemented with cylindrical source acoustic geometry, linked to a bioheat equation (e.g., in one embodiment, using the Arrhenius equation). FIG. 43

shows the results of a KZK simulation of cylindrical transducer output showing linear superposition of multiple pulses; approximately the same temperatures are reached when treating with 3 pulses of 0.45 J or 1 pulse of 1.35 J ($3 \times 0.45 \text{ J}$). The results of a theoretical experiment with one embodiment of a band therapy system as shown in FIG. 43, suggest non-linear acoustics are not a major contributor to the final temperature for the energies, and suggests that body tissue acts as a linear time-invariant system, which allows for simplification of the heat transfer physics, and the heating and cooling rates to be described in relatively few parameters. In various embodiments, a therapy system with a hand wand 100 includes a module 200 with one or more ultrasound transducers 280. In some embodiments, an ultrasound transducer 280 includes one or more cylindrical ultrasound elements 281, as shown in FIGs. 5A - 8. The cylindrical transducer element 281 is configured for bulk heating treatments with its linear focus along an axis, resulting in a continuous line that can be moved with an automated motion mechanism to treat a rectangular plane. In one embodiment, lines of treatment are deposited perpendicular to the direction of motor movement in a single direction. A single "pass" of treatment creates a number of therapy lines equal to $\{\text{Length}\} / \{\text{Spacing}\}$.

[00291] In various embodiments, various cylindrical geometries were tested from the first build (4.5 MHz - 12 mm width at 4.5 mm and 6.0 mm depths); however, acoustic tank testing showed higher acoustic pressures (and therefore heating rates) at the each edge of the therapy line. In one embodiment, a ceramic transducer was apodized to produce a flat thermal profile, as shown in FIGs. 44 and 45. In various embodiments, different cylindrical geometries based on two operating frequencies, two treatment widths, and two treatment depths were built: (1) 3.5 MHz – 22 mm Width - 4.5 mm Depth; (2) 3.5 MHz – 22 mm Width - 6.0 mm Depth; (3) 4.5 MHz – 22 mm Width - 4.5 mm Depth; (4) 4.5 MHz – 22 mm Width - 6.0 mm Depth; (5) 3.5 MHz – 12 mm Width - 4.5 mm Depth; (6) 4.5 MHz – 12 mm Width - 4.5 mm Depth; (7) 3.5 MHz – 12 mm Width - 6.0 mm Depth; and (8) 4.5 MHz – 12 mm Width - 6.0 mm Depth. In various embodiments, a tissue temperature measurement system included one or more of including IR thermography, temperature strips, and resistance temperature detectors (RTDs), and thermocouples. IR thermography can be used to read skin surface temperatures. Temperature strips are able to provide peak

temperature reached. RTD sheaths have a large thermal mass and may have a slow response time. In various embodiments, thermocouples have a response time less than a second, which is helpful for measuring the heating and cooling phase of a single treatment pass. Thermocouples also have the advantage of being small enough that they can be positioned through a large bore needle to the desired tissue depth. In one embodiment, a particular isoeffective dose is attached via the heating phase followed by a maintenance phase in which the system or an operator pulses treatment at an interval to sustain a steady state temperature. A parameter of interest during this phase is the average pulse period needed to maintain the steady state temperature.

[00292] Body Contouring via Ultrasound Band Therapy

[00293] In various embodiments, a band therapy system is configured for body contouring. In one embodiment, body contouring treatment involves thermal heat shock concurrent with, and/or followed by apoptosis. In one embodiment, body contouring treatment involves exposing fat to 42-55°C for 1-5 minutes to induce delayed apoptosis. In one embodiment, body contouring treatment involves exposing fat at a focus depth of at least 13 mm below the skin surface.

[00294] Temperature and Dose Control

[00295] In various embodiments, one or more sensors may be included in the module 200 or system 20 to measure a temperature. In one embodiment, methods of temperature and/or dose control are provided. In one embodiment, temperature is measured to control dosage of energy provided for a tissue treatment. In various embodiments, a temperature sensor is used to measure a tissue temperature to increase, decrease, and/or maintain the application of energy to the tissue in order to reach a target temperature or target temperature range. In some embodiments, a temperature sensor is used for safety, for example, to reduce or cease energy application if a threshold or maximum target temperature is reached. In one embodiment, a cooling device or system can be employed to cool a tissue temperature if a certain temperature is reached. In some embodiments, a

temperature sensor is used to modulate an energy dose, for example, via modulation, termination of amplitude, power, frequency, pulse, speed, or other factors.

[00296] In one embodiment, a temperature sensor is used to measure a skin surface temperature. In one embodiment, a temperature sensor may be positioned on top of the transducer holder and a sensor may be located in a portion of the module, or vice versa (swapped). In various embodiments, a temperature sensor is positioned on a system or module housing, such as in one embodiment, near or on an acoustic window, such as an acoustically transparent member 230. In one embodiment, one or more temperature sensors are positioned around or proximate an acoustically transparent member 230. In one embodiment, one or more temperature sensors are positioned in or on an acoustically transparent member 230. In one embodiment, a temperature sensor measure from a skin surface can be used to calculate a temperature in a tissue at the focus depth of the energy application. In various embodiments, a target tissue temperature can be calculated and/or correlated to the depth in tissue, type of tissue (e.g. epidermis, dermis, fat, etc.) and relative thickness of tissue between the skin surface and the focus depth. In some embodiments, a temperature sensor provides a temperature measurement for a signal to a control system. In some embodiments, a temperature sensor provides a temperature measurement for visual and/or auditory feedback to a system operator, such as a text, color, flash, sound, beep, alert, alarm, or other sensory indicator of a temperature state.

[00297] In some embodiments, imaging can be used to control energy dose. In one embodiment, a thermal lens effect can be used to account for speckle shift and/or feature shift to indicate a temperature of a tissue at a target location, such as at a focus depth in tissue below the skin surface. In one embodiment, Acoustic Radiation Force Impulse (ARFI) imaging is used to calculate a tissue temperature. In one embodiment, Shear Wave Elasticity Imaging (SWEI) is used to calculate a tissue temperature. In one embodiment, attenuation is used to calculate a tissue temperature.

[00298] In various embodiments, a variable dose delivery technique is used to attain a target temperature in a tissue and maintain that target temperature. The body temperature at a depth in tissue surrounds a thermal treatment zone (TTZ). In one embodiment, to overcome the body temperature, a treatment focuses energy at the TTZ at a first rate to bring the tissue temperature in the TTZ to a target temperature. Once that target temperature is attained, the second rate can be reduced or stopped to maintain the tissue at the target temperature.

[00299] In some embodiments, energy is focused at a depth or position in tissue at the TTZ, such that the temperature in the focal zone is increased. However, at the edges (e.g., ends, top, bottom, sides, etc.) of the focal zone, a boundary condition at body temperature can result in temperature fluctuations at the boundaries of the treatment area 552. In various embodiments, movement of the TTZ 550 can be with the transducer delivering energy to create a treatment area 552. In one embodiment, a movement mechanism 285 can automatically move the cylindrical transduction element 281 across the surface of a treatment area so that the TTZ 550 can form a treatment area 552. In FIG. 53, the treatment area 552 is surrounded at the edges by body temperature, or approximately body temperature. In some embodiments, the temperature in the treatment area 552 along the edges/boundary is lower than the desired, target temperature.

[00300] In various embodiments, mechanical velocity modulation is used to attain a specific thermal distribution in the treatment area 552. In one embodiment, in order to attain a more uniform temperature in the treatment area 552, the applied temperature at the edges/boundaries is increased to counteract the surrounding body temperature difference. FIG. 54 illustrates an embodiment of mechanical velocity modulation in which the velocity, or speed of the automatic motion of the motion mechanism moving the transducer along direction 290 (along the elevation direction), is varied to provide a more uniform temperature in the treatment area 552 by slowing near the boundaries, resulting in increased temperature at the boundaries (start and stop position, such as along a 25 mm travel distance, in one embodiment). The increased velocity near the middle delivers a lower temperature than the decreased velocity.

[00301] In various embodiments, amplitude modulation is used to attain a specific thermal distribution in the treatment area 552. In one embodiment, in order to attain a more uniform temperature in the treatment area 552, the applied temperature at the edges/boundaries is increased to counteract the surrounding body temperature difference. FIG. 55 illustrates an embodiment of amplitude modulation in which the amplitude (correlates to power) of the energy delivered by the transducer as the automatic motion of the motion mechanism moves along direction 290 (along the elevation direction), is varied to provide a more uniform temperature in the treatment area 552 by increasing amplitude near the boundaries, resulting in increased temperature at the boundaries (start and stop position, such as along a 25 mm travel distance, in one embodiment). The lower amplitude near the middle delivers a lower temperature than the higher amplitude near the boundaries.

[00302] In various embodiments, aperture apodization is used to attain a specific thermal distribution in the treatment area 552. In one embodiment, aperture apodization along the non-focused dimension (such as along TTZ 550 and/or the azimuth direction) is used in order to attain a more uniform temperature in the treatment area 552. The applied temperature at the end points, along the edges/boundaries is increased to counteract the surrounding body temperature difference. FIG. 56 illustrates an embodiment of aperture apodization in which the amplitude of the energy delivered by the transducer along the TTZ 550 is varied to provide a more uniform temperature in the treatment area 552 by increasing amplitude near the end points near the boundaries, resulting in increased temperature at the boundaries (with L as a length of the focused line TTZ 550, $L/2$ from center is the end point). The lower amplitude near the middle delivers a lower temperature than the higher amplitude near the boundaries. In various embodiments, a temperature profile can be generated along the TTZ with embodiments of a coated transduction element 600, such as illustrated in FIGs. 31-38.

[00303] In various embodiments, pulsing and/or duty cycles are controlled to attain a specific thermal distribution in the treatment area 552. At FIG. 57, in various embodiments, treatment patterns can have a consistent or a constant pulsing or duty

cycle. At FIG. 58, in various embodiments, treatment patterns can have variable pulsing or a variable duty cycle, with variations in any of peak amplitude, spacing of application, duration of application. As shown in FIG. 58, the application of energy is longer and covers more area near the boundary of the treatment area 552, while the internal region has less power application for a corresponding lower temperature application in the internal region.

[00304] In various embodiments, treatment patterns are used to attain a specific thermal distribution in the treatment area 552. In some embodiments the TTZ 550 has a dimension (e.g., width, height, thickness, etc.). In some embodiments, the pulsed application of TTZ 550 is non-overlapping, as shown in FIG. 59. In some embodiments, the pulsed application of TTZ 550 is overlapping, as is shown near a boundary in FIG. 60, where the amount of overlapping can be constant or vary. As shown in the embodiment in FIG. 60, the amount of overlap varies and includes a non-overlapping portion. In various embodiments, a cross hatching pattern is used, wherein the system hand piece is rotated about 90 degrees, or orthogonally, and the motion mechanism is operated in one or more additional passes over a target tissue region in an orthogonal direction to a prior treatment pass.

[00305] In various embodiments, a specific thermal distribution in the treatment area 552 comprises treatment with a tissue temperature of 37 - 50°C for a duration of minutes to hours to cause a targeted percentage of cell death (such as fat cell death) which a relationship can be determined via Arrhenius equation, such as is shown on the left side of FIG. 61. In various embodiments, a specific thermal distribution in the treatment area 552 comprises treatment with a tissue temperature of over 60°C for a duration of seconds to fractions of a second (or near instantaneous) coagulation, ablation, and/or cell death (such as fat cell death) at the elevated temperature, such as shown on the right side of FIG. 62. In various embodiments, a treatment can be either one, or both in sequence and/or simultaneous treatments.

[00306] In some embodiments, one, two, three, four, or more of mechanical velocity modulation, amplitude modulation, aperture apodization, pulsing duty cycles, and/or treatments at different temperatures can be used to achieve a desired

temperature profile across the treatment area 552. In various embodiments, one or more of mechanical velocity modulation, amplitude modulation, aperture apodization, pulsing duty cycles, and/or treatments at different temperatures is used to create a temperature profile, wherein the temperature profile can include areas for increased, decreased, and/or uniform temperatures. In some embodiments, one, two, or more types of treatment are applied in one, two, or three dimensions (along any of the azimuth, elevation, and/or depth directions) and is configured for treatment in any of one, two, or three dimensions to create a one, two, or three dimensional temperature profile.

[00307] In some embodiments, a compound lens system produces various peak intensities and different depths. In various embodiments, a mechanical and/or electronic focus lens can be used in any one or more of the azimuth, elevation, and/or depth directions. As illustrated in FIG. 62 and FIG. 63, a compound lens system can create two or more focal lines 550 and 550a.

[00308] In various embodiments, an ultrasound system 20 comprises a motion mechanism 285 configured for moving a plurality of ultrasound transducers 280 and/or a plurality of ultrasound elements 281. In some embodiments, such as illustrated in an embodiment at FIG. 64, the motion mechanism 285 is configured to minimize heat fluctuation in treated tissue and reduce treatment time by presenting the plurality of elements 281 on a conveyor system, such as with a belt and/or pulley system that can move the plurality of elements 281 at a velocity v . In various embodiments, velocity can be constant, variable, zero (e.g., stopped), reversible (e.g., forward and backward, left and right, first direction and second direction, etc.) and/or have values in the range 0 - 100 RPM, 1 RPM - 50 RPM, or other velocities. In various embodiments, the velocity is any value 1 - 1,000 cm/second (e.g., 10, 20, 50, 100, 200, 500, 1000 cm/sec, and any other values therein). In various embodiments, the motion mechanism 285 moves one, two, three, four, five, six, seven, eight, or more ultrasound elements 281. In various embodiments, ultrasound elements 281 are connected, or spaced at a distance of 0.01-10 cm apart, (e.g., 0.1, 0.5, 1, 2, 5 cm and any values therein), such that one, two, or more ultrasound elements 281 are configured to treat a treatment area.

[00309] In some embodiments, imaging is used to confirm the quality of the acoustic coupling between a treatment device and the skin. In one embodiment, clarity of an ultrasound image along a treatment area, line, or point is used to determine the extent to which a device is acoustically coupled to a skin surface. In one embodiment, defocused imaging and/or Voltage Standing Wave Ratio (VSWR) from backscatter is used to check acoustic coupling for a treatment.

[00310] In some embodiments, a treatment is automated. In one embodiment, a treatment is set up by acoustically coupling a system to a skin surface, and the movement mechanism and treatment is automated to function. In various embodiments, the system is coupled to a skin surface via suction. In various embodiments, a system operator couples the system to a skin surface, activates the system, and can leave the system to automatically perform a treatment, or a portion of a treatment. In one embodiment, a system uses suction and/or vacuum pressure to hold a probe or portion of the system to a skin surface, allowing the system user to initiate treatment and leave the system to automatically perform a treatment or a portion of a treatment for a period of time. In some embodiments, a treatment system includes a TENS stimulation device to reduce pain at a skin treatment site.

[00311] In particular embodiments, said tissue to be treated is selected from facial tissue, frontal neck tissue and chest tissue (décolletage). In particular such embodiments, said ultrasound is applied using a set of conditions as shown in Table 2.

[00312] In such embodiments, a clostridial neurotoxin is applied using a set of conditions depending on depth and size of the muscles in the corresponding tissue areas. In particular embodiments, from 1 to 6 U of the neurotoxic component of Botulinum toxin are injected into each of between 1 and 30 different points of said tissue area.

[00313] In particular embodiments, said tissue area is a skin area of face, neck (frontal neck), or chest (décolletage). In particular embodiments, said tissue area is the platysma muscle.

[00314] In particular such embodiment, said clostridial neurotoxin is applied using the following set of conditions: 30 – 60 U of the neurotoxic component of Botulinum toxin are injected superficially into 15-30 points of the skin of the platysma.

[00315] In such an embodiment, said ultrasound is applied using the set of conditions shown for “Frontal Neck” in Table 2.

[00316] In particular other embodiments, the muscle tissue is selected from:

- M. depressor anguli oris, which is used for treating marionette lines. Botulinum toxin type A is injected with each 5 U into both sides;
- M. mentalis, which is used for smoothing the chin area. Botulinum toxin type A is injected with max. 6 U into the middle area of the muscle or with each 3 U into both sides of the muscle.
- M. orbicularis oris, which is used for smoothing the upper lip fold;
- M. buccinators, which is used for smoothing the cheek area. Botulinum toxin type A is injected with 1 U per injection into 5 – 6 injection sites distributed over the muscle; and
- M. orbicularis oculi, which is used for smoothing crows’ feet. Botulinum toxin type A is injected with 4 U per injection around the muscle; the injections do not exceed totally 12 units.

EXAMPLES

Example 1: Treatment of Platysma using Botulinum toxin A:

[00317] A patient has a laxity of the platysma area or another photoaged skin area and is treated with an injection of 30 – 60 U of the neurotoxic component of BoNT/A (Xeomin®) superficially into 15-30 points of the skin of the platysma, i.e. 2 units every two centimetre along the band. The larynx area has to be spared.

[00318] After 3 days/, the patient is treated by application of ultrasound using the using the set of conditions shown for “Frontal Neck” in Table 2.

[00319] 2 – 3 weeks after application of the ultrasound treatment, the skin starts showing a smoother appearance without reduced exhibition of distinct platysma muscle bands any more due to the beginning neocollagenesis and the subsequent tightening of the tissue. This process is fully completed after 3 two 6 months.

Example 2: Treatment of Platysma using a recombinant Botulinum toxin of SEQ ID 9:

[00320] A patient has a laxity of the platysma area or another photoaged skin area and is treated with injections of a botulinum toxin obtained from the precursor protein according to SEQ ID No 9 superficially into 15-30 points of the skin of the platysma. The larynx area has to be spared.

[00321] After 1 day, the patient is treated by application of ultrasound using the set of conditions shown for “Frontal Neck” in Table 2.B.

[00322] After 2 – 3 weeks after application of the ultrasound treatment, the skin starts showing a smoother appearance without reduced exhibition of distinct platysma muscle bands any more due to the beginning neocollagenesis and the subsequent tightening of the tissue. This process is fully completed after 3 two 6 months.

[00323] The following examples are comparative examples generically showing the application of band transducers:

Comparative Example 4:

[00324] As illustrated at FIGS. 11A - 20, it was experimentally verified that an embodiment of a transducer 280 comprising a cylindrical transduction element 281, which was applied to a simulated target tissue, an artificial tissue, and to porcine

tissue sample, formed localized, linear thermal treatment zone (TTZ 550) in a targeted focal area 552. In the experiment, the single cylindrical transduction element 281 was constructed with a radius and focal depth of 15 mm. The size of the cylindrical transduction element 281 was 20 mm (azimuth) by 17 mm (elevation). Additional focal gain could be achieved with a larger aperture. Depth is limited by frequency and focal gain, and was set to 6 mm below a simulated tissue surface.

[00325] In FIGS. 11A-13B, treatment profiles were plotted based on theoretical and experimental performance with a cylindrical transduction element 281. The normalized pressure is proportional to a thermal heating measure at the specified depth. The spikes (pointed regions at the top of the plots) plots indicate pressure peaks that occur as a result of the geometric edge effects of the geometry of the cylindrical transduction element 281. The spikes are visible in both the theoretical and the experimental performance results. The software simulated experiments reflect the theoretical performance of the 15 mm cylindrical transduction element 281 in FIGS. 11A, 12A, 13A, 14A, 15A, and 16A. The physical experiments in simulated tissue were performed and measured, with results in FIGS. 11B, 12B, 13B, 14B, 15B and 16B.

[00326] In FIGS. 11A - 11B and 14A-14B, the depth is 20 mm, where the normalized pressure peaks at a value of roughly 0.15. As shown in FIG. 14A-14B, the normalized pressure is not visible. In FIGS. 12A - 12B and 15A-15B, the depth is the designed, optimal 15 mm, where the normalized pressure peaks at a value of roughly 0.8. As shown in FIG. 15A-15B, the normalized pressure is clearly visible, with peak normalized pressures at approximately 0.9 - 1.0. The size of the cylindrical transduction element 281 was 20 mm (azimuth) by 17 mm (elevation). The size of the TTZ 550 at a depth of 15 mm was about 0.5 mm thick (along azimuth) by 17 mm width (along elevation). In FIGS. 13A - 13B and 16A-16B, the depth is 13 mm, where the normalized pressure peaks at a value of roughly 0.25. As shown in FIG. 16A-16B, the normalized pressure is barely visible. As shown through both the theoretical and experimental data, the normalized pressure corresponding to the TTZ 550 for a 15 mm focal depth cylindrical transduction element 281 is at the 15 mm depth, with a linear TTZ 550.

[00327] As illustrated at FIGS. 17 - 20, it was experimentally verified that the embodiment of a transducer 280 comprising a cylindrical transduction element 281, which was applied to a porcine tissue sample (muscle tissue), formed localized, linear thermal treatment zone (TTZ 550) in a targeted focal area 552. In the experiment, an embodiment of a transducer 280 comprising a cylindrical transduction element 281 was passed over the porcine muscle tissue with three passes in 20 seconds, operating at 4.5 MHz and a tissue depth of 6 mm. As shown in FIG. 17, the three passes (shown with the three spikes in temperature) increased the temperature of the porcine muscle. Two power levels are shown. The 40 W porcine muscle started at 30°C, and over the course of 20 seconds (between the 20 and 40 second marks) of heating through three passes of the cylindrical transduction element 281 over the target tissue region, the temperature spiked to a maximum of about 55°C, then gradually cooled to about 32°C 100 seconds after the start of the treatment. The 60 W porcine muscle started at about 24°C, and over the course of 20 seconds (between the 40 and 60 second marks) of heating through three passes of the cylindrical transduction element 281 over the target tissue region, the temperature spiked to a maximum of about 59°C, then gradually cooled to about 40°C about 80 seconds after the start of the treatment.

[00328] FIG. 18 is a photograph of the porcine muscle after treatment confirming line and plane heating. In one embodiment, the coagulation was dependent on time-off between lines, time-off between passes, and number of passes. Slower temperature rise than thermal coagulation points. FIG. 19 is a cross-section cut through the porcine muscle in FIG. 18 showing a linear thermal treatment zone. FIG. 20 is an orthogonal cross-section cut through the porcine muscle in FIG. 19 showing a planar thermal treatment zone.

Comparative Example 5:

[00329] As illustrated at FIGS. 28 - 30, it was experimentally verified that an embodiment of a partially coated transducer 600 comprising a cylindrical transduction element 281, which was applied to a simulated target tissue, formed a localized,

linear thermal treatment zone (TTZ 550) in a targeted focal area 552. The partially coated transducer 600 includes a first coated region 287 that fully plates the concave surface 282 of the cylindrical transduction element and at least a second coated region 287 that partially plates the convex surface 283 of the cylindrical transduction element. Both the first and the second coated regions 287 of the partially coated transducer 600 are plated with silver. In the experiment, the single cylindrical transduction element 281 was constructed with a radius and focal depth of 15 mm. The size of the cylindrical transduction element 281 was 20 mm (azimuth) by 17 mm (elevation). The cylindrical transduction element 281 had an opening 285 in the center of 4mm in diameter.

[00330] In FIGS. 28, 29 and 30, treatment profiles were plotted based on theoretical performance with a cylindrical transduction element 281. The theoretical performance is proportional the thermal heating at the specified depth. The software simulated experiment reflects the theoretical performance of the 15 mm partially coated transducer 600, showing a consistent linear thermal treatment zone 550 at the 15 mm depth.

Comparative Example 6:

[00331] Multiple in-vivo porcine studies and multiple cadaver studies were conducted to evaluate various embodiments of hardware to perform bulk heating treatments. Early studies focused on specifying and improving the instrumentation necessary to measure subdermal temperatures. In some embodiments, insulated wire thermocouples were placed at focal and subfocal depths by snaking the thermocouple through a needle-bored hole in the skin and verifying the depth with a Siemens s2000 ultrasound device. Temperature profiles were collected using a high sampling DAQ card. Once the measurement setup was defined, a replicated 3-factor 3-level design of experiments was performed in the in-vivo porcine model to determine energy settings that could safely reach isoeffective dosages without causing skin surface damage. In one embodiment, a mean temperature differential of 10°C was observed, with a mean focal heating rate of -1.2°C/pass. Safe heating rates appear to be similar across transducer.

[00332] A thermal dosage study was performed in the in-vivo porcine model after safe heating rates were determined. The study demonstrated an embodiment of the system is capable of reaching isoeffective dosages such as 47°C for 3 minutes, 48°C for 1 minute, and 50°C for 1 minute without exceeding 41°C on the skin surface. In some embodiments, use of higher temperature, shorter exposure time treatments may have the potential to overshoot the target temperature and could overheat the skin surface. In various embodiments, the longer it takes to perform an isoeffective dose, the more heat diffuses to the surrounding tissue and less selective the treatment becomes with depth. Additionally, the longer the isoeffective exposure time, the more impractical the treatment becomes from an operator and ergonomics point of view. For these reasons, in some embodiments, use of higher isoeffective temperatures and shorter exposure times were preferred.

[00333] In-vivo porcine tests were conducted to determine if the candidate treatment settings for submental could cause adverse surface skin effects. The animals procured for these studies were light skinned, 120-140 pound castrated male Yucatan miniature pigs, selected due to its skin characteristics being similar to that of human tissue. Skin surface data was evaluated by monitoring the animal for evidence of erythema, edema, and contusion on the skin surface after treatment. Photographs of each treatment area were taken prior to and following treatment (Canon G9 and Canon VIXIA HF 510). In one embodiment, a thermal dosage study using a cylindrical element transducer was performed on in-vivo porcine models. In several embodiments, test sites were able to achieve a significant temperature differential between the focus tissue site and the skin surface without causing damage to the skin surface. FIG. 46 shows the temperature profiles from an embodiment of an in-vivo porcine model treatment in which the temperature profile reached 50°C for several seconds without the skin surface exceeding 41°C, and shows a temperature differential of as much as 15°C between the focus tissue site and the skin surface. The temperature change accrued from a single pass of treatment is sufficiently small (approximately 0.9°C/pass or 0.13°C/sec) to perform corrective action and maintain a target temperature within +/-1°C. A modified 3-factor 3-level design of experiments was performed in the in-vivo porcine model to

determine a range of energy settings that could safely reach the isoeffective dosages temperatures shown in FIG. 42. The settings, according to various embodiments, are tabulated in the table at FIG. 47. The Design of Experiments (DOE) tests an acoustic power range of 10-20 W, exposure times of 20-40 ms, and spacings in the range of 0.1 - 0.3 mm. FIG. 48 shows an embodiment of a treatment setting that was able to achieve a relatively high thermal dosage at the focus with little to no dose or temperature increase at the skin surface. The focus achieves a thermal dose of 100 equivalent minutes (red-dashed line) at $T=43^{\circ}\text{C}$ on the 24th pass, which corresponds to a theoretical survival fraction of 1 % according to FIG. 42. In various embodiments, similar temperature rises and heating rates were achieved at the focus and surface across various embodiments of transducers for treatments that did not cause significant skin surface damage. A mean temperature differential of 10°C was observed, with a mean focal heating rate of $-1.2^{\circ}\text{C/pass}$. The largest temperature differential between the focus and the skin was achieved by the 3.5 MHz, 22 mm width, 6.0 depth design which had an average difference of 12°C across treatments. Since the heating rates that produce little to no surface effects are similar across transducer, the 3.5 MHz, 22 mm width, 6.0 mm depth transducer was selected to be assessed in a thermal dosage study.

[00334] In various embodiments, thermal dosage studies were performed on in-vivo porcine and cadaver models to determine safe isoeffective dosages, and the geometry of adipocyte death through histological evaluation. The Table at FIG. 49 tabulates the target time-temperature exposures to achieve different levels of adipocyte death. According to the empirical data in FIG. 42, Site 2 and 5 should achieve little to no adipocyte death. Sites 3, 6 and 7 should achieve a high degree of adipocyte death. Sites 1 and 4 are within the transition region and should achieve a moderate amount of adipocyte death. The table at FIG. 50 lists the energy settings used to approach each isoeffective dose using a 3.5 MHz, 22 mm width, 6.0 mm depth transducer. In various embodiments, treatments were active for 2-3 minutes with 20-30 pulses to reach the target temperature with a 1 degree Celsius/pass ramp followed by maintenance pulses ever 3-5 seconds. A few test sites showed mild surface effects the day of treatment, only to become more pronounced as the injury rose to the skin surface. FIG. 51 shows one site that was treated aggressively for the

purpose of coagulating tissue for histological control through overdosing. In the embodiment in FIG. 51, the dimension of the lesion represents an example of the spread of thermal energy, measuring 12.6 x 19.9 mm on the skin surface with a depth of edema that can be detected up to 12 mm from the skin surface. A visual representation of the time-temperature goals listed in the table at FIG. 49 is shown in FIG. 52 (triangle marks), with six isoeffective dosages achieved in the lab are overlaid in FIG. 52 (square marks). Two of these isoeffective dosages fall in the coagulative region, two fall in the transition region, and two in the hyperthermia region.

[00335] Some embodiments and the examples described herein are examples and not intended to be limiting in describing the full scope of compositions and methods of these invention(s). Equivalent changes, modifications and variations of some embodiments, materials, compositions and methods can be made within the scope of the embodiments herein. In various embodiments, a device or method can combine features or characteristics of any of the embodiments disclosed herein.

[00336] While the invention is susceptible to various modifications, and alternative forms, specific examples thereof have been shown in the drawings and are herein described in detail. It should be understood, however, that the invention is not to be limited to the particular forms or methods disclosed, but to the contrary, the invention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the various embodiments described and the appended claims. Any methods disclosed herein need not be performed in the order recited. The methods disclosed herein include certain actions taken by a practitioner; however, they can also include any third-party instruction of those actions, either expressly or by implication. For example, actions such as "coupling an ultrasound probe to a skin surface" include "instructing the coupling of an ultrasound probe to a skin surface." The ranges disclosed herein also encompass any and all overlap, sub-ranges, and combinations thereof. Language such as "up to," "at least," "greater than," "less than," "between," and the like includes the number recited. Numbers preceded by a

term such as "about" or "approximately" include the recited numbers. For example, "about 25 mm" includes "25 mm." The terms "approximately", "about", and "substantially" as used herein represent an amount or characteristic close to the stated amount or characteristic that still performs a desired function or achieves a desired result. For example, the terms "approximately", "about", and "substantially" may refer to an amount that is within less than 10% of, within less than 5% of, within less than 1% of, within less than 0.1% of, and within less than 0.01% of the stated amount or characteristic.

Table 1: Sequences**SEQ ID NO 1: Neurotoxic component of BoNT/A, sequence of single-chain precursor**

```

MPFVNKQFNY KDPVNGVDIA YIKIPNVGQM QPVKAFKIHN KIWVIPERDT
FTNPEEGDLN PPPEAKQVPV SYDSTYLST DNEKDNLYKG VTKLFERIYS
TDLGRMLLTS IVRGIPFWGG STIDTELKVI DTNCINVIQP DGSYRSEELN
LVIIGPSADI IQFECKSFGH EVLNLTRNGY GSTQYIRFSP DFTFGFEESL
EVDTNPLLGA GKFDTPAVT LAHELIHAGH RLYGIAINPN RVFKVNTNAY
YEMSGLEVSE EELRTFGGHD AKFIDSLQEN EFRLYYYNKF KDIASLTNKA
KSIVGTTASL QYMKNVFEKE YLLSEDTSGK FSVDKLKFDK LYKMLTEIYT
EDNFVKFFKV LNRKTYLNFD KAVFKINIVP KVNITYIDGF NLRNTNLAAN
FNGQNTTEINN MNFTKLKNFT GLFEFYKLLC VRGIITSKTK SLDKGYNKAL
NDLCIKVNNW DLFFSPSEDN FTNDLNKGEE ITSDTNIEAA EENISLDLIQ
QYYLTFNFDN EPENISIENL SSDIIGQLEL MPNIERFPNG KKYELDKYTM
FHYLRAQEFE HGKSRIALTN SVNEALLNPS RVYTFSSDY VKKVNKATEA
AMFLGWVEQL VYDFTDETSE VSTDKIADI TIIIPYIGPA LNIGNMLYKD
DFVGALIFSG AVILLEFIPE IAIPVLGTFA LVSYIANKVL TVQTDNALS
KRNEKWDEVY KYIVTNWLAK VNTQIDLIRK KMKEALENQA EATKAIINYQ
YNQYTEEEKN NINFNIDDL SSKNESINKA MININKFLNQ CSVSYLMNSM
IPYGVKRLD FDASLKDALL KYIYDNRGTL IGQVDRKDK VNNLTSTDIP
FQLSKYVDNQ RLLSTFTEYI KNIINTSILN LRYESNHLID LSRYSKINI
GSKVNFDPID KNQIQLFNLE SSKIEVILKN AIVYNSMYEN FSTSFWRIP
KYFNSISLNN EYTIINCME NSGWKVS LN GEIITWLQDT QEIKQRVVFK
YSQMINISDY INRWIFVTIT NNRLNNSKIY INGRLLIDQKP ISNLGNIHAS
NNIMFKLDGC RDTHRYIWIK YFNLFDEKELN EKEIKDLYDN QNSGILKDF
WGDYLQYDKP YYMLNLYDPN KYVDVNNVGI RGYMYLKGPR GSVMTTNIYL
NSSLYRGTKF IIKKYASGNK DNIVRNNDRV YINVVVKNKE YRLATNASQA
GVEKILSALE IPDVGNLSQV VVMKSKNDQG ITNKCKMNLQ DNNGNDIGFI
GFHQFNNAIAK LVASNWNVRQ IERSSRTLGC SWEFIPVDDG WGERPL

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SEQ ID NO 2: Neurotoxic component of BoNT/B, sequence of single-chain precursor

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MPVTINNFFNY NDPIDNNNII MMEPPFARGT GRYYKAFKIT DRIWIIPERY
TFGYKPEDFN KSSGIFNRDV CEYYPDPYLN TNDKKNIFLQ TMIKLFNRIK
SKPLGEKLLI MIINGIPYLG DRRVPLEEFN TNIASVTVNK LISNPGEVER
KKGIFANLII FGGPVLNEN ETIDIGIQNH FASREGFGGI MQMKFCPEYV
SVFNNVQENK GASIFNRRGY FSDPALILMH ELIHVLHGLY GIKVDDLPIV
PNEKKFFMQS TDAIQAEELY TFGGQDPSII TPSTDKSIYD KVLQNFGRIV
DRLNKVLVCI SDPNININII KNKFKDKYKF VEDSEGKYSI DVESFDKLYK
SLMFGFTETN IAENYKIKTR ASYFSDSLPP VKIKNLLDNE IYTIEEGFNI
SDKDMEKEYR GONKAINKQA YEEISKEHLA VYKIQMCKSV KAPGICIDVD
NEDLFFIADK NSFSDDL SKN ERIEYNTQSN YIENDFPINE LILDTDLISK
IELPSENTES LTDFNVDPV YEKQPAIKKI FTDENTIFQY LYSQTFPLDI
RDISLTSSFD DALLFSNKVY SFFSMDYIKT ANKVVEAGLF AGWVKQIVND
FVIEANKSNT MDKIADISLI VPIYGLALNV GNETAKGNFE NAFEIAGASI
LLEFIPELLI PVVGAFLLES YIDNKNKIIK TIDNALTKRN EKWSDMYGLI
VAQWLSTVNT QFYTIKEGMY KALNYQAQAL EEI IKYRYNI YSEKEKSNIN
IDFNDINSKL NEGINQAIDN INNFINGCSV SYLMKKMIPL AVEKLLDFDN
TLKKNLLNYI DENKLYLIGS AEYEKSKVNK YLKTIMPFDL SIYTNDTILI
EMFNKYNSEI LNNIILNLRY KDNLLIDLSG YGAKVEVYDG VELNDKNQFK
LTSSANSKIR VTQNQNIIFN SVFLDFSVSF WIRIPKYKND GIQNYIHNEY
TIINC MKNNS GWKISIRGNR IIWTLIDING KTKSVFFEYN IREDISEYIN
RWFVVTITNN LNNAKIYING KLESNTDIKD IREVIANGEI IFKLDGDIDR
TQFIWMKYFS IFNTELSQSN IEERYKIQSY SEYLKDFWGN PLMYNKEYYM
FNAGNKNSYI KLKKDSPVGE ILTRSKYNQN SKYINYRDLY IGEKFIIRK
SNSQSINDDI VRKEDIYILD FFNLNQEW RV YTYKYFKKEE EKLFLAPISD

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SDEFYNTIQI KEYDEQPTYS CQLLFKKDEE STDEIGLIGI HRFYESGIVF
 EEYKDYFCIS KWYLKEVKRK PYNLKLGCNW QFIPKDEGWT E

SEQ ID NO 3: Neurotoxic component of BoNT/C1, sequence of single-chain precursor

MPITINNFNY SDPVDNKNIL YLDTHLNTLA NEPEKAFRIT GNIWVIPDRF
 SRNSNPNLNK PPRVTSPKSG YYDPNYLSTD SDKDPFLKEI IKLFKRINSR
 EIGEELIYRL STDIPFPGNN NTPINTFDFD VDFNSVDVKT RQGNNWVKTG
 SINPSVIITG PRENIIDPET STFKLNTNTF AAQEGFGALS IISISPRFML
 TYSNATNDVG EGRFSKSEFC MDPILILMHE LNHAMHNLYG IAIPNDQTIS
 SVTSNIFYSQ YNVKLEYAEI YAFGGPTIDL IPKSARKYFE EKALDYYSI
 AKRLNSITTA NPSSFNKYIG EYKQKLIRKY RFVVESSGEV TVNRNKFVEL
 YNELTQIFTE FNYAKIYNVQ NRKIYLSNVY TPVTANILDD NVYDIQNGFN
 IPKSNLNVLF MGQNLNRNPA LRKVNPNENML YLFTKFCHKA IDGRSLYNKT
 LDCRELLVKN TDLPPFIDIS DVKTDIFLRK DINEETEVYI YPDNVSDVQV
 ILSKNTSEHG QLDLLYPSID SESEILPGEN QVFYDNRTQN VDYLSNYYYYL
 ESQKLSDNVE DFTFTRSIEE ALDNSAKVYT YFPTLANKVN AGVQGGFLFM
 WANDVVEDFT TNILRKDTLD KISDVSAIIP YIGPALNISN SVRRGNFTEA
 FAVTGVTILL EAFPEFTIPA LGAFVIYSKV QERNEIIKTI DNCLEQRIKR
 WKDSYEWMMG TWLSRIITQF NNISYQMYDS LNYQAGAIKA KIDLEYKKYS
 GSDKENIKSQ VENLKNSLDV KISEAMNNIN KFIRESVITY LFKNMLPKVI
 DELNEFDRNT KAKLINLIDS HNIILVGEVD KLKAKVNNSF QNTIPFNIFS
 YTNSLLKDI INEYFNNIND SKILSLQNRK NTLVDTSGYN AEVSEEGDVQ
 LNPIFPDFDK LGSSGEDRGK VIVTQENIV YNSMYESFSI SFWIRINKWV
 SNLPGYTIID SVKNNSGWSI GIISNFLVFT LKQNEDEQS INFSDISNN
 APGYNKWWFFV TVTNNMMGMN KIYINGKLID TIKVKELTGI NFSKTITFEI
 NKIPDTGLIT SDSDNINMWI RDFYIFAKEL DGKDINILFN SLQYTNVVKD
 YWGNDLRYNK EYYMVNIDYL NRYMYANSRQ IVFNTRNNN DFNEGYKIII
 KRIRGNTNDT RVRGGDILYF DMTINNKAYN LFMKNETMYA DNHSTEDIYA
 IGLREQTKDI NDNIIFQIQP MNNTYYYASQ IFKSNFNGEN ISGICSIGTY
 RFRLGGDWYR HNYLVPTVKQ GNYASLLEST STHWGFVPVS E

SEQ ID NO 4: Neurotoxic component of BoNT/D, sequence of single-chain precursor

MTWPVKDFNY SDPVNDNDIL YLRIPQNKLI TTPVKAFFMIT QNIWVIPERF
 SSDTNPSLSK PPRPTSQYQS YYDPSYLSTD EQKDTFLKGI IKLFKRINER
 DIGKKLINYL VVGSPFMGDS STPEDTFDFT RHTTNIAVEK FENGSKVVTN
 IITPSVLIFG PLPNILDYTA SLTLQGQQSN PSFEGFGTSL ILKVAPEFLI
 TFSDVTSNQS SAVLGKSIIFC MDPVIALMHE LTHSLHQLYG INIPSDKRIR
 PQVSEGGFSQ DGPVNVQFEEL YTFGGDLVEI IPQIERSQLR EKALGHYKDI
 AKRLNNINKT IPSSWISNID KYKKIFSEKY NFDKDNTGNF VVNIDKFNSL
 YSDLTNVMSE VVYSSQYNVK NRTHYFSRHY LPVFANILDD NIYTIRDGFN
 LTNKGFNIEN SGQNIERNPA LQKLSSSESV DLFTKVCLRL TKNSRDDSTC
 IKVKNRRLPY VADKDSISQE IFENKIITDE TNVQNYSDKF SLDESILDGQ
 VPINPEIVDP LLPNVNMEPL NLPGEIIVFY DDITKYVDYL NSYYLESQK
 LSNNVENITL TTSVEEALGY SNKIYTFLPS LAEKVNKGVO AGLFLNWANE
 VVEDFTTNIM KKDTLDKISD VSVIIPYIGP ALNIGNSALR GNFNQAFATA
 GVAFLLEGFP EFTIPALGVF TFYSSIQERE KIIKTIENCL EQRVKRWKDS
 YQWMVSNWLS RITTQFNHIN YQMYDSLSYQ ADAIKAKIDL EYKKYSGSDK
 ENIKSQVENL KNSLDVKISE AMNNINKFIR ECSVTYLFKN MLPKVIDELN
 KFDLRTKTEL INLIDSHNII LVGEVDRLKA KVNESFENTM PFNIFSYTNN
 SLLKDIINEY FNSINDSKIL SLQNKKNALV DTSGYNAEVR VGDNVQLNTI
 YTNDFKLSSS GDKIIVNLNN NILYSAIYEN SSVSFWIKIS KDLTNSHNEY
 TIINSIEQNS GWKLCIRNGN IEWILQDVNR KYKSLIFDYS ESLSHTGYTN
 KWFFVTITNN IMGYMKLYIN GELKQSQKIE DLDEVKLDKT IVFGIDENID
 ENQMLWIRDF NIFSKELSNE DINIVYEQI LRNVIKDYWG NPLKFDTEYY

IINDNYIDRY IAPESNVVLV VQYPDRSKLY TGNPITIKSV SDKNPYSRIL
 NGDNIIHLML YNSRKYMIIR DTDTIYATQG GECSQNCVYA LKLQSNLGNV
 GIGIFSINKI VSKNKYCSQI FSSFRENTML LADIYKPWRF SFKNAYTPVA
 VTNYETKLLS TSSFWKFISR DPGWVE

SEQ ID NO 5: Neurotoxic component of BoNT/E, sequence of single-chain precursor

MPKINSFNYN DPNVNDRTILY IKPGGCQEFY KSFNIMKNIW IIPERNVIGT
 TPQDFHPPTS LKNGDSSYYD PNYLQSDEEK DRFLKIVTKI FNRINNNLSG
 GILLEELSKA NPYLGNNDTP DNQFHIGDAS AVEIKFSNGS QDILLPNVII
 MGAEPDLFET NSSNISLRNN YMPSNHRFGS IAIVTFSPEY SFRFNDNCMN
 EFIQDPALTL MHELIHSLHG LYGAKGITTK YTITQKQNPL ITNIRGTNIE
 EFLTFGGTDL NIITSAQSND IYTNLLADYK KIASKLSKVQ VSNPLLNPYK
 DVFEAKYGLD KDASGIYSVN INKFNDIFKK LYSFTEFDLR TKFQVKCRQT
 YIGQYKYFKL SNLLNDSIYN ISEGYNINNL KVNFRGQAN LNPRIITPIT
 GRGLVKKIIR FCKNIVSVKG IRKSICIEIN NGELFFVASE NSYNDNINT
 PKEIDDTVTS NNNYENDLDQ VILNFNSES A PGLSDEKLNLT TIQNDAYIPK
 YDSNGTSDIE QHDVNELNVF FYLDAQKQVPE GENNVNLTSS IDTALLEQPK
 IYTFSSSEFI NNVNKPQVAA LEVSWIQQVL VDFTEANQK STVDKIADIS
 IVVPYIGLAL NIGNEAQKGN FKDALELLGA GILLEFEPEL LIPTILVFTI
 KSFGLSSDNK NKKVIKAINNA LKERDEKWE VYSFIVSNWM TKINTQFNKR
 KEQMYQALQN QVNAIKTIE SKYNSYTL EE KNELTNKYDI KQIENELNQK
 VSIAMNNIDR FLTESISYSL MKIINEVKIN KLREYDENVK TYLLNYIIQH
 GSILGESQQE LNSMVTDTLN NSIPFKLSSY TDDKILISYF NKFFKRIKSS
 SVLNMRYKND KYVDTSGYDS NININGDVYK YPTNKNQFGI YNDKLSEVNI
 SQNDYIIIDN KYKNFSISFW VRIPNYDNKI VNVNNEYTII NCMRDNNSGW
 KVS LNHNH EII WTFEDNRGIN QKLAFNYGNA NGISDYINKW IFVTITNDRL
 GDSKLYINGN LIDQKSILNL GNIHVSDNIL FKIVNCSYTR YIGIRYFNIF
 DKELDETEIQ TLYSNEPNTN ILKDFWGNYL LYDKEYYLLN VLKPNNFIDR
 RKDSTLSINN IRSTILLANR LYSGIKVKIQ RVNNSSTNDN LVRKNDQVYI
 NFVASKTHLF PLYADTATTN KEKTIKISSS GNRFNQVVVM NSVGNCMTMF
 KNNNGNIGL LGFKADTVVA STWYYTHMRD HTNSNGCFWN FISEEHGWQE
 K

SEQ ID NO 6: Neurotoxic component of BoNT/F, sequence of single-chain precursor

MPVAINSFNY NDPVNDDTIL YMQIPYEEKS KKYYKA FEIM RNVWIIIPERN
 TIGTNPSDFD PPASLKNSS AYYDPNYLTT DAEKDRYLKT TIKLFKRINS
 NPAGKVLLQE ISYAKPYLGN DHTPIDFESP VTRTTSVNIK LSTNVES SML
 LNLLVLGAGP DIFESCCYPV RKLIDPDVVY DPSNYGFGSI NIVTFSPEYE
 YTFNDISGGH NSSTESFIAD PAISLAHELI HALHGLYGAR GVTYEETIEV
 KQAPLMIAEK PIRLEEFLTF GGQDLNIITS AMKEKIYNNL LANYEKIATR
 LSEVNSAPPE YDINEYKDYF QWKYGLDKNA DGSYTVNENK FNEIYKKLYS
 FTESDLANKF KVKCRNTYFI KYEFLKVPNL LDDDIYTVSE GFNIGNLAVN
 NRGQSIKLP KIIDSIPDKG LVEKIVKFC SVIPRKGTKA PPRLCIRVNN
 SELFFVASES SYNENDINTP KEIDDTTNLN NNYRNNLDEV ILDYNSTIP
 QISNRTLNTL VQDNSYVPRY DSNGTSEIEE YDVVDFNVFF YLHAQKVPEG
 ETNISLTSSI DTALLEESKD IFFSSEFIDT INKPVNAALF IDWISKVIRD
 FTTEATQKST VDKIADISLI VPIVGLALNI IEAEKGNFE EAFELLGVGI
 LLEFVPELTI PVILVFTIKS YIDSYENKNK AIKAINNSLI EREAKWKEIY
 SWIVSNWLTR INTQFNKRKE QMYQALQNQV DAIKTAIEYK YNNYTSDEKN
 RLESEYNINN IEELNKKVS LAMKNIERFM TESSISYLMK LINEAKVGKL
 KKYDNHVKSD LLNYILDHRS ILGEQTNELS DLVTSTLNSS IPFELSSYTN
 DKILIIYFNR LYKKIKDSSI LDMRYENNKF IDISGYGSNI SINGNVYIYS
 TNRNQFGIYN SRLSEVNIAQ NNDIIYNSRY QNFSSISFWVR IPKHYKPMNH
 NREYTIINCM GNNNSGWKIS LRTVRDCEII WTLQDTSGNK ENLIFRYEEL
 NRISNYINKW IFVTITNNRL GNSRIYINGN LIVEKSISNL GDIHVSDNIL
 FKIVGCDDDET YVGIRYFKVF NTELDKTEIE TLYSNEPDPS ILKNYWGNYL

LYNKKYYLFN LLRKDKYITL NSGILNINQQ RGVTEGSVFL NYKLYEGVEV
 IIRKNGPIDI SNTDNFVRKN DLAYINVVDR GVEYRLYADT KSEKEKIIRT
 SNLNDSLQOI IVMDSIGNNC TMNFQNNNGS NIGLLGFHSN NLVASSWYYN
 NIRRNTSSNG CFWSSISKEN GWKE

SEQ ID NO 7: Neurotoxic component of BoNT/G, sequence of single-chain precursor

MPVNIKXFNY NDPINDDII MMEPFNDPGP GTYYKAFRII DRIWIVPERF
 TYGFQPDQFN ASTGVFSKDV YEYDPTYLK TDAEKDKFLK TMIKLFNRIN
 SKPSGQRLLD MIVDAIPYLG NASTPPDKFA ANVANVSINK KIIQPGAEDQ
 IKGLMTNLII FGP GPVLSN FTDSMIMNGH SPISEGFGAR MMIRFCPSCL
 NVFNNVQENK DTSIFSRRAY FADPALTMH ELIHVLHGLY GIKISNLPIT
 PNTKEFFMQH SDPVQAEELY TFGGHDPVI SPSTDMNIYN KALQNFQDIA
 NRLNIVSSAQ GSGIDISLYK QIYKNKYDFV EDPNGKYSVD KDKFDKLYKA
 LMFGFTETNL AGEYGIKTRY SYFSEYLPPI KTEKLLDNTI YTQNEGFNIA
 SKNLKTEFNG QNKAVNKEAY EEISLEHLVI YRIAMCKPVM YKNTGKSEQC
 IIVNNEDLFF IANKDSFSKD LAKAETIAYN TQNNTIENNF SIDQLILDND
 LSSGIDL PNE NTEPFTNFDD IDIPVYIKQS ALKKIFVDGD SLFEYLHAQT
 FPSNIENLQL TNSLNDALRN NNKVYTFST NLVEKANTVV GASLFVNWVK
 GVIDDFTSES TQKSTIDKVS DVSIIIPYIG PALNVGNETA KENFKNAFEI
 GGAAILMEFI PELIVPIVGF FTLESYVGNK GHIIMTISNA LKKRDQKWD
 MYGLIVSQWL STVNTQFYTI KERMYNALNN QSQAIIEIIE DQYNRYSEED
 KMNINIDFND IDFKLNQ SIN LAINNIDDFI NQCSISYLMN RMIPLAVKKL
 KDFDDNLKRD LLEYIDTNEL YLLDEVNLIK SKVNRHLKDS IPFDLSLYTK
 DTILIQVFNN YISNISSNAI LSLSYRGGR LIDSSGYGATM NVGSDVIFND
 IGNQGFKLNN SENSNITAHQ SKFVVYDSMF DNFSINFWR TPKYNNNDIQ
 TYLQNEYTII SCIKNDSGWK VSIKGNRIIW TLIDVNAKSK SIFFEYSIKD
 NISDYINKWF SITITNDR LG NANIYINGSL KKSEKILNLD RINSSNDIDF
 KLINCTDTTK FVWIKDFNIF GRELNATEVS SLYWISSTN TLKDFWGNPL
 RYDTQYYLFN QGMQNIYIKY FSKASMGETA PRTNFNNAI NYQNL YLGLR
 FIIKKASNSR NINNDNIVRE GDYIYLNIDN ISDESYRVYV LVNSKEIQQT
 LFLAPINDDP TFYDVLQIKK YYEKT TYNQ ILCEKDTKTF GLFGIGKFVK
 DYGYVWD TYD NYFCISQWYL RRISENINKL RLGCNWQFIP VDEGWTE

SEQ ID NO 8: Neurotoxic component of TxNT, sequence of single-chain precursor

MPITINNFRY SDPVNNDTII MMEPPYCKGL DIYYKAFKIT DRIWIVPERY
 EFGTKPEDFN PPSSLIEGAS EYD PNYLRT DSKDRFLQT MVKLFNRIKN
 NVAGEALLDK IINAIPYLG SYSLLDKFDT NSNSVSFNL EQDPGATTK
 SAMLTNLIIF GPGPVLNKNE VRGIVLRVDN KNYFPCRDGF GSIMQMAFCP
 EYVPTFDNVI ENITSLTIGK SKYFQDPALL LMHELIHVLH GLYGMQVSSH
 EIIPSKQEIY MQHTYPISAE ELFTFGGQDA NLISIDIKND LYEKTLDNDYK
 AIANKLSQVT SCNDPNIDID SYKQIYQQKY QFDKDSNGQY IVNEDKFQIL
 YNSIMYG FTE IELGKKFNIK TRLSYFSMNH DPVKIPNLLD DTIYNDTEGF
 NIESKDLKSE YKQNM RVNT NAFRNVDGSG LVSKLIGLCK KIIPPTNIRE
 NLYNRTASLT DLGGELCIKI KNEDLTFIAE KNSFSEEPFQ DEIVSYNTKN
 KPLNFNYS LD KIIVDYNLQS KITLPNDRTT PVTKGIPYAP EYKSNAASTI
 EIHNDNTI YQYLYAQKSP TTLQRITMTN SVDDALINST KIYSYFPSVI
 SKVNQGAQGI LFLQWVRDII DDFTNESSQK TTIDKISDVS TIVPYIGPAL
 NIVKQGYEGN RYGALETTGV VLLLEYIPEI TLPVIAALSI AESSTQKEKI
 IKTIQDFLEK FIEKIEWYK LVKAKWLGTV NTQFQKRSYQ MYRSLEYQVD
 AIKKIIDY EY KIYSGPDKEQ IADEINN LKN KLEEKANKAM ININIFMRES
 SRSFLVNQMI NEAKQ LLEF DTQSKN ILMQ YIKANSKFIG ITELKKLESK
 INKVFSTPIP FSYSKNLDCW VDNEEDIDVI LKKSTILNLD INNDIISDIS
 GFNSSVITYP DAQLVPGING KAIHLVN NES SEVIVHKAMD IEYNDMFNNF
 TVSFWRVPK VSASHLEQYG TNEYSIISM KKHSLSIGSG WSVSLKGNNL
 IWTLKDSAGE VRQITFRDLP DKFNAYLANK WVFITITNDR LSSANLYING

VLMGSAEITG LGAIREDNNI TLKLDRCNNN NQYVSIDKFR IFCKALNPKE
 IEKLYTSYLS ITFLRDFWGN PLRYDTEYYL IPVASSSKDV QLKNITDYM
 LTNAPSYTNG KLNIIYYRRLY NGLKFIKRY TPNNEIDSFV KSGDFIKLYV
 SYNNEHIVG YPKDGNFNN LDRILRVGYN APGIPLYKKM EAVKLRLDKT
 YSVQLKLYDD KNASLGLVGT HNGQIGNDPN RDILIASNWX FNHLKDKILG
 CDWYFVPTDE GWTND

SEQ ID NO 9: Neurotoxic component of botulinum neurotoxin subtype E with reduced persistence (variant 1), sequence of single-chain precursor

Met Pro Lys Ile Asn Ser Phe Asn Tyr Asn Asp Pro Val Asn Asp Arg
 Thr Ile Leu Tyr Ile Lys Pro Gly Gly Cys Gln Glu Phe Tyr Lys Ser
 Phe Asn Ile Met Lys Asn Ile Trp Ile Ile Pro Glu Arg Asn Val Ile
 Gly Thr Thr Pro Gln Asp Phe His Pro Pro Thr Ser Leu Lys Asn Gly
 Asp Ser Ser Tyr Tyr Asp Pro Asn Tyr Leu Gln Ser Asp Glu Glu Lys
 Asp Arg Phe Leu Lys Ile Val Thr Lys Ile Phe Asn Arg Ile Asn Asn
 Asn Leu Ser Gly Gly Ile Leu Leu Glu Glu Leu Ser Lys Ala Asn Pro
 Tyr Leu Gly Asn Asp Asn Thr Pro Asp Asn Gln Phe His Ile Gly Asp
 Ala Ser Ala Val Glu Ile Lys Phe Ser Asn Gly Ser Gln Asp Ile Leu
 Leu Pro Asn Val Ile Ile Met Gly Ala Glu Pro Asp Leu Phe Glu Thr
 Asn Ser Ser Asn Ile Ser Leu Arg Asn Asn Tyr Met Pro Ser Asn His
 Gly Phe Gly Ser Ile Ala Ile Val Thr Phe Ser Pro Glu Tyr Ser Phe
 Arg Phe Asn Asp Asn Ser Met Asn Glu Phe Ile Gln Asp Pro Ala Leu
 Thr Leu Met His Glu Leu Ile His Ser Leu His Gly Leu Tyr Gly Ala
 Lys Gly Ile Thr Thr Lys Tyr Thr Ile Thr Gln Lys Gln Asn Pro Leu
 Ile Thr Asn Ile Arg Gly Thr Asn Ile Glu Glu Phe Leu Thr Phe Gly
 Gly Thr Asp Leu Asn Ile Ile Thr Ser Ala Gln Ser Asn Asp Ile Tyr
 Thr Asn Leu Leu Ala Asp Tyr Lys Lys Ile Ala Ser Lys Leu Ser Lys
 Val Gln Val Ser Asn Pro Leu Leu Asn Pro Tyr Lys Asp Val Phe Glu
 Ala Lys Tyr Gly Leu Asp Lys Asp Ala Ser Gly Ile Tyr Ser Val Asn
 Ile Asn Lys Phe Asn Asp Ile Phe Lys Lys Leu Tyr Ser Phe Thr Glu
 Phe Asp Leu Ala Thr Lys Phe Gln Val Lys Cys Arg Gln Thr Tyr Ile
 Gly Gln Tyr Lys Tyr Phe Lys Leu Ser Asn Leu Leu Asn Asp Ser Ile
 Tyr Asn Ile Ser Glu Gly Tyr Asn Ile Asn Asn Leu Lys Val Asn Phe
 Arg Gly Gln Asn Ala Asn Leu Asn Pro Arg Ile Ile Thr Pro Ile Thr
 Gly Arg Gly Leu Val Lys Lys Ile Ile Arg Phe Cys Val Arg Gly Ile
 Ile Thr Ser Leu Thr Phe Glu His Asn Trp Ala Gln Leu Glu Asn Lys
 Ser Leu Val Pro Arg Gly Ser Lys Ala Leu Asn Asp Leu Cys Ile Glu
 Ile Asn Asn Gly Glu Leu Phe Phe Val Ala Ser Glu Asn Ser Tyr Asn
 Asp Asp Asn Ile Asn Thr Pro Lys Glu Ile Asp Asp Thr Val Thr Ser
 Asn Asn Asn Tyr Glu Asn Asp Leu Asp Gln Val Ile Leu Asn Phe Asn

Ser Glu Ser Ala Pro Gly Leu Ser Asp Glu Lys Leu Asn Leu Thr Ile
 Gln Asn Asp Ala Tyr Ile Pro Lys Tyr Asp Ser Asn Gly Thr Ser Asp
 Ile Glu Gln His Asp Val Asn Glu Leu Asn Val Phe Phe Tyr Leu Asp
 Ala Gln Lys Val Pro Glu Gly Glu Asn Asn Val Asn Leu Thr Ser Ser
 Ile Asp Thr Ala Leu Leu Glu Gln Pro Lys Ile Tyr Thr Phe Phe Ser
 Ser Glu Phe Ile Asn Asn Val Asn Lys Pro Val Gln Ala Ala Leu Phe
 Val Ser Trp Ile Gln Gln Val Leu Val Asp Phe Thr Thr Glu Ala Asn
 Gln Lys Ser Thr Val Asp Lys Ile Ala Asp Ile Ser Ile Val Val Pro
 Tyr Ile Gly Leu Ala Leu Asn Ile Gly Asn Glu Ala Gln Lys Gly Asn
 Phe Lys Asp Ala Leu Glu Leu Leu Gly Ala Gly Ile Leu Leu Glu Phe
 Glu Pro Glu Leu Leu Ile Pro Thr Ile Leu Val Phe Thr Ile Lys Ser
 Phe Leu Gly Ser Ser Asp Asn Lys Asn Lys Val Ile Lys Ala Ile Asn
 Asn Ala Leu Lys Glu Arg Asp Glu Lys Trp Lys Glu Val Tyr Ser Phe
 Ile Val Ser Asn Trp Met Thr Lys Ile Asn Thr Gln Phe Asn Lys Arg
 Lys Glu Gln Met Tyr Gln Ala Leu Gln Asn Gln Val Asn Ala Ile Lys
 Thr Ile Ile Glu Ser Lys Tyr Asn Ser Tyr Thr Leu Glu Glu Lys Asn
 Glu Leu Thr Asn Lys Tyr Asp Ile Lys Gln Ile Glu Asn Glu Leu Asn
 Gln Lys Val Ser Ile Ala Met Asn Asn Ile Asp Arg Phe Leu Thr Glu
 Ser Ser Ile Ser Tyr Leu Met Lys Leu Ile Asn Glu Val Lys Ile Asn
 Lys Leu Arg Glu Tyr Asp Glu Asn Val Lys Thr Tyr Leu Leu Asn Tyr
 Ile Ile Gln His Gly Ser Ile Leu Gly Glu Ser Gln Gln Glu Leu Asn
 Ser Met Val Thr Asp Thr Leu Asn Asn Ser Ile Pro Phe Lys Leu Ser
 Ser Tyr Thr Asp Asp Lys Ile Leu Ile Ser Tyr Phe Asn Lys Phe Phe
 Lys Arg Ile Lys Ser Ser Ser Val Leu Asn Met Arg Tyr Lys Asn Asp
 Lys Tyr Val Asp Thr Ser Gly Tyr Asp Ser Asn Ile Asn Ile Asn Gly
 Asp Val Tyr Lys Tyr Pro Thr Asn Lys Asn Gln Phe Gly Ile Tyr Asn
 Asp Lys Leu Ser Glu Val Asn Ile Ser Gln Asn Asp Tyr Ile Ile Tyr
 Asp Asn Lys Tyr Lys Asn Phe Ser Ile Ser Phe Trp Val Arg Ile Pro
 Asn Tyr Asp Asn Lys Ile Val Asn Val Asn Asn Glu Tyr Thr Ile Ile
 Asn Cys Met Arg Asp Asn Asn Ser Gly Trp Lys Val Ser Leu Asn His
 Asn Glu Ile Ile Trp Thr Leu Gln Asp Asn Ala Gly Ile Asn Gln Lys
 Leu Ala Phe Asn Tyr Gly Asn Ala Asn Gly Ile Ser Asp Tyr Ile Asn
 Lys Trp Ile Phe Val Thr Ile Thr Asn Asp Arg Leu Gly Asp Ser
 Lys Leu Tyr Ile Asn Gly Asn Leu Ile Asp Gln Lys Ser Ile Leu
 Asn Leu Gly Asn Ile His Val Ser Asp Asn Ile Leu Phe Lys Ile
 Val Asn Cys Ser Tyr Thr Arg Tyr Ile Gly Ile Arg Tyr Phe Asn
 Ile Phe Asp Lys Glu Leu Asp Glu Thr Glu Ile Gln Thr Leu Tyr
 Ser Asn Glu Pro Asn Thr Asn Ile Leu Lys Asp Phe Trp Gly Asn
 Tyr Leu Leu Tyr Asp Lys Glu Tyr Tyr Leu Leu Asn Val Leu Lys

Pro Asn Asn Phe Ile Asp Arg Arg Lys Asp Ser Thr Leu Ser Ile
 Asn Asn Ile Arg Ser Thr Ile Leu Leu Ala Asn Arg Leu Tyr Ser
 Gly Ile Lys Val Lys Ile Gln Arg Val Asn Asn Ser Ser Thr Asn
 Asp Asn Leu Val Arg Lys Asn Asp Gln Val Tyr Ile Asn Phe Val
 Ala Ser Lys Thr His Leu Phe Pro Leu Tyr Ala Asp Thr Ala Thr
 Thr Asn Lys Glu Lys Thr Ile Lys Ile Ser Ser Ser Gly Asn Arg
 Phe Asn Gln Val Val Val Met Asn Ser Val Gly Asn Asn Cys Thr
 Met Asn Phe Lys Asn Asn Asn Gly Asn Asn Ile Gly Leu Leu Gly
 Phe Lys Ala Asp Thr Val Val Ala Ser Thr Trp Tyr Tyr Thr His
 Met Arg Asp His Thr Asn Ser Asn Gly Cys Phe Trp Asn Phe Ile
 Ser Glu Glu His Gly Trp Gln Glu Lys

SEQ ID NO 10: Neurotoxic component of botulinum neurotoxin subtype E with reduced persistence (variant 2), sequence of single-chain precursor

Met Pro Lys Ile Asn Ser Phe Asn Tyr Asn Asp Pro Val Asn Asp Arg
 Thr Ile Leu Tyr Ile Lys Pro Gly Gly Cys Gln Glu Phe Tyr Lys Ser
 Phe Asn Ile Met Lys Asn Ile Trp Ile Ile Pro Glu Arg Asn Val Ile
 Gly Thr Thr Pro Gln Asp Phe His Pro Pro Thr Ser Leu Lys Asn Gly
 Asp Ser Ser Tyr Tyr Asp Pro Asn Tyr Leu Gln Ser Asp Glu Glu Lys
 Asp Arg Phe Leu Lys Ile Val Thr Lys Ile Phe Asn Arg Ile Asn Asn
 Asn Leu Ser Gly Gly Ile Leu Leu Glu Glu Leu Ser Lys Ala Asn Pro
 Tyr Leu Gly Asn Asp Asn Thr Pro Asp Asn Gln Phe His Ile Gly Asp
 Ala Ser Ala Val Glu Ile Lys Phe Ser Asn Gly Ser Gln Asp Ile Leu
 Leu Pro Asn Val Ile Ile Met Gly Ala Glu Pro Asp Leu Phe Glu Thr
 Asn Ser Ser Asn Ile Ser Leu Arg Asn Asn Tyr Met Pro Ser Asn His
 Gly Phe Gly Ser Ile Ala Ile Val Thr Phe Ser Pro Glu Tyr Ser Phe
 Arg Phe Asn Asp Asn Ser Met Asn Glu Phe Ile Gln Asp Pro Ala Leu
 Thr Leu Met His Glu Leu Ile His Ser Leu His Gly Leu Tyr Gly Ala
 Lys Gly Ile Thr Thr Lys Tyr Thr Ile Thr Gln Lys Gln Asn Pro Leu
 Ile Thr Asn Ile Arg Gly Thr Asn Ile Glu Glu Phe Leu Thr Phe Gly
 Gly Thr Asp Leu Asn Ile Ile Thr Ser Ala Gln Ser Asn Asp Ile Tyr
 Thr Asn Leu Leu Ala Asp Tyr Lys Lys Ile Ala Ser Lys Leu Ser Lys
 Val Gln Val Ser Asn Pro Leu Leu Asn Pro Tyr Lys Asp Val Phe Glu
 Ala Lys Tyr Gly Leu Asp Lys Asp Ala Ser Gly Ile Tyr Ser Val Asn
 Ile Asn Lys Phe Asn Asp Ile Phe Lys Lys Leu Tyr Ser Phe Thr Glu
 Phe Asp Leu Ala Thr Lys Phe Gln Val Lys Cys Arg Gln Thr Tyr Ile
 Gly Gln Tyr Lys Tyr Phe Lys Leu Ser Asn Leu Leu Asn Asp Ser Ile

Tyr Asn Ile Ser Glu Gly Tyr Asn Ile Asn Asn Leu Lys Val Asn Phe
Arg Gly Gln Asn Ala Asn Leu Asn Pro Arg Ile Ile Thr Pro Ile Thr
Gly Arg Gly Leu Val Lys Lys Ile Ile Arg Phe Cys Val Arg Gly Ile
Ile Thr Ser Leu Thr Phe Glu His Asn Trp Ala Gln Leu Thr Ser Lys
Ser Leu Val Pro Arg Gly Ser Lys Ala Leu Asn Asp Leu Cys Ile Glu
Ile Asn Asn Gly Glu Leu Phe Phe Val Ala Ser Glu Asn Ser Tyr Asn
Asp Asp Asn Ile Asn Thr Pro Lys Glu Ile Asp Asp Thr Val Thr Ser
Asn Asn Asn Tyr Glu Asn Asp Leu Asp Gln Val Ile Leu Asn Phe Asn
Ser Glu Ser Ala Pro Gly Leu Ser Asp Glu Lys Leu Asn Leu Thr Ile
Gln Asn Asp Ala Tyr Ile Pro Lys Tyr Asp Ser Asn Gly Thr Ser Asp
Ile Glu Gln His Asp Val Asn Glu Leu Asn Val Phe Phe Tyr Leu Asp
Ala Gln Lys Val Pro Glu Gly Glu Asn Asn Val Asn Leu Thr Ser Ser
Ile Asp Thr Ala Leu Leu Glu Gln Pro Lys Ile Tyr Thr Phe Phe Ser
Ser Glu Phe Ile Asn Asn Val Asn Lys Pro Val Gln Ala Ala Leu Phe
Val Ser Trp Ile Gln Gln Val Leu Val Asp Phe Thr Thr Glu Ala Asn
Gln Lys Ser Thr Val Asp Lys Ile Ala Asp Ile Ser Ile Val Val Pro
Tyr Ile Gly Leu Ala Leu Asn Ile Gly Asn Glu Ala Gln Lys Gly Asn
Phe Lys Asp Ala Leu Glu Leu Leu Gly Ala Gly Ile Leu Leu Glu Phe
Glu Pro Glu Leu Leu Ile Pro Thr Ile Leu Val Phe Thr Ile Lys Ser
Phe Leu Gly Ser Ser Asp Asn Lys Asn Lys Val Ile Lys Ala Ile Asn
Asn Ala Leu Lys Glu Arg Asp Glu Lys Trp Lys Glu Val Tyr Ser Phe
Ile Val Ser Asn Trp Met Thr Lys Ile Asn Thr Gln Phe Asn Lys Arg
Lys Glu Gln Met Tyr Gln Ala Leu Gln Asn Gln Val Asn Ala Ile Lys
Thr Ile Ile Glu Ser Lys Tyr Asn Ser Tyr Thr Leu Glu Glu Lys Asn
Glu Leu Thr Asn Lys Tyr Asp Ile Lys Gln Ile Glu Asn Glu Leu Asn
Gln Lys Val Ser Ile Ala Met Asn Asn Ile Asp Arg Phe Leu Thr Glu
Ser Ser Ile Ser Tyr Leu Met Lys Leu Ile Asn Glu Val Lys Ile Asn
Lys Leu Arg Glu Tyr Asp Glu Asn Val Lys Thr Tyr Leu Leu Asn Tyr
Ile Ile Gln His Gly Ser Ile Leu Gly Glu Ser Gln Gln Glu Leu Asn
Ser Met Val Thr Asp Thr Leu Asn Asn Ser Ile Pro Phe Lys Leu Ser
Ser Tyr Thr Asp Asp Lys Ile Leu Ile Ser Tyr Phe Asn Lys Phe Phe
Lys Arg Ile Lys Ser Ser Ser Val Leu Asn Met Arg Tyr Lys Asn Asp
Lys Tyr Val Asp Thr Ser Gly Tyr Asp Ser Asn Ile Asn Ile Asn Gly
Asp Val Tyr Lys Tyr Pro Thr Asn Lys Asn Gln Phe Gly Ile Tyr Asn
Asp Lys Leu Ser Glu Val Asn Ile Ser Gln Asn Asp Tyr Ile Ile Tyr
Asp Asn Lys Tyr Lys Asn Phe Ser Ile Ser Phe Trp Val Arg Ile Pro
Asn Tyr Asp Asn Lys Ile Val Asn Val Asn Asn Glu Tyr Thr Ile Ile
Asn Cys Met Arg Asp Asn Asn Ser Gly Trp Lys Val Ser Leu Asn His
Asn Glu Ile Ile Trp Thr Leu Gln Asp Asn Ala Gly Ile Asn Gln Lys

Leu Ala Phe Asn Tyr Gly Asn Ala Asn Gly Ile Ser Asp Tyr Ile Asn
 Lys Trp Ile Phe Val Thr Ile Thr Asn Asp Arg Leu Gly Asp Ser
 Lys Leu Tyr Ile Asn Gly Asn Leu Ile Asp Gln Lys Ser Ile Leu
 Asn Leu Gly Asn Ile His Val Ser Asp Asn Ile Leu Phe Lys Ile
 Val Asn Cys Ser Tyr Thr Arg Tyr Ile Gly Ile Arg Tyr Phe Asn
 Ile Phe Asp Lys Glu Leu Asp Glu Thr Glu Ile Gln Thr Leu Tyr
 Ser Asn Glu Pro Asn Thr Asn Ile Leu Lys Asp Phe Trp Gly Asn
 Tyr Leu Leu Tyr Asp Lys Glu Tyr Tyr Leu Leu Asn Val Leu Lys
 Pro Asn Asn Phe Ile Asp Arg Arg Lys Asp Ser Thr Leu Ser Ile
 Asn Asn Ile Arg Ser Thr Ile Leu Leu Ala Asn Arg Leu Tyr Ser
 Gly Ile Lys Val Lys Ile Gln Arg Val Asn Asn Ser Ser Thr Asn
 Asp Asn Leu Val Arg Lys Asn Asp Gln Val Tyr Ile Asn Phe Val
 Ala Ser Lys Thr His Leu Phe Pro Leu Tyr Ala Asp Thr Ala Thr
 Thr Asn Lys Glu Lys Thr Ile Lys Ile Ser Ser Ser Gly Asn Arg
 Phe Asn Gln Val Val Val Met Asn Ser Val Gly Asn Asn Cys Thr
 Met Asn Phe Lys Asn Asn Asn Gly Asn Asn Ile Gly Leu Leu Gly
 Phe Lys Ala Asp Thr Val Val Ala Ser Thr Trp Tyr Tyr Thr His
 Met Arg Asp His Thr Asn Ser Asn Gly Cys Phe Trp Asn Phe Ile
 Ser Glu Glu His Gly Trp Gln Glu Lys

Table 2: Conditions for Application of Ultherapy®**A. Standard Ultherapy® Settings**

[00337] The existing Ultherapy® systems uses ultrasound transducers operating at different frequencies (4 MHz, as in DS4-4.5; 7 MHz, as in DS7-4.5, DS7-3.0, DS7-3.0N; and 10 MHz, as in DS10-1.5, DS10-1.5N) and targeting different depths (4.5 mm; 3.0 mm; 1.5 mm), wherein an ultrasound transducer is linearly moved along the desired treatment lines to apply the ultrasound. The transducers listed in the following table are all commercially available.

Tissue to be treated	Lines	Treatment duration	Depth	Treatment area	Treatment region(s) per area on each side	Lines per area on each side	Transducer	Figure
Face	800	75 min	4.5 mm	Brow	1	10	DS7-4.5	65
				Lateral orbit	2	5 / 5		
				Infraorbital	na	na	na	
				Cheek	2	60 / 60		
				Upper neck	3	15 / 25 / 15	DS4-4.5	
			3.0 mm	Brow	1	25	DS7-3.0/DS7-3.0N	66
				Lateral orbit	2	5 / 5		
				Infraorbital	1	15		
				Cheek	3	15 / 40 / 40	DS7-3.0	
				Upper neck	4	5 / 15 / 25 / 15		
1.5 mm	Brow	1	15	DS10-1.5/DS10-1.5N	67			
	Lateral orbit	2	7.5 / 7.5					
	Infraorbital	1	15					

				WO 2017/063743	
			Area 2 next to area 1	1	20
			Area 3 next to area 2	1	16
		1.5 mm	Area 1 below sternoclavicular notch parallel to sternum	1	20
			Area 2 next to area 1	na	
			Area 3 next to area 2	na	
					DS10-1.5

B. Modified Ultherapy® Settings

[00338] The modified Ultherapy® systems uses ultrasound transduction systems, which comprise a cylindrical transduction element, which is configured to apply ultrasonic energy to a linear focal zone at a focal depth. As for the conventional transducers, these modified ultrasound transducers operate at different frequencies (4 MHz, 7 MHz, and 10 MHz) and target different focal zone depths (4.5 mm; 3.0 mm; 1.5 mm), but apply ultrasound as treatment lines. The number of lines and the treatment areas are as defined above in Table 2.A.

CLAIMS

1. A clostridial neurotoxin for use in the treatment of a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, wherein said treatment comprises the steps of (i) applying said clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of the body associated with high muscle tension; and (ii) applying ultrasound to the tissue treated with said clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used that is configured to apply ultrasonic energy to a linear focal zone at a focal depth.
2. A method of treating a patient with tissue exhibiting a loss of tightness, in particular photoaged tissue, comprising the steps of (i) applying a clostridial neurotoxin to one or more muscles in said tissue, in particular in skin areas situated in areas of said tissue associated with high muscle tension; and (ii) applying ultrasound to the tissue treated with said clostridial neurotoxin, wherein in step (ii) an ultrasound transduction system is used that is configured to apply ultrasonic energy to a linear focal zone at a focal depth.
3. The clostridial neurotoxin for use in a treatment according to claim 1, or the method according to claim 2, wherein in step (ii) an ultrasound transduction system is used comprising:
 - a cylindrical transduction element; and
 - a power source configured to drive the cylindrical transduction element,wherein the cylindrical transduction element is configured to apply ultrasonic energy to a linear focal zone at a focal depth.

4. The clostridial neurotoxin for use in a treatment according to claim 1 or 3, or the method according to claim 2 or 3, wherein in step (i) from 1 to 6 U of the neurotoxic component of Botulinum toxin are injected into each of between 1 and 30 different points of said tissue.
5. The clostridial neurotoxin for use in a treatment according to any one of claims 1 and 3 to 4, or the method according to any one of claims 2 to 4, wherein said tissue is selected from platysma, frown line, marionette line, and décolletage, in particular platysma.
6. The clostridial neurotoxin for use in a treatment according to claim 5, or the method according to claim 5, wherein in step (i) 30 – 60 U of the neurotoxic component of Botulinum toxin are injected superficially by injection of between 1 and 2 U into each of 15-30 points of the skin of the platysma.
7. The clostridial neurotoxin for use in a treatment according to any one of claims 1 and 3 to 6, or the method according to any one of claims 2 to 6, wherein said ultrasound is applied to heat a treatment area in said tissue at the focal depth to a temperature in a range between 40 - 65°C.
8. The clostridial neurotoxin for use in a treatment according to claim 7, or the method according to claim 7, wherein in step (ii), ultrasound is applied to said tissue by selecting one or more areas in said tissue, particularly one or more areas with between 4 and 9 cm², particularly squares of between 4 and 9 cm², particularly squares with 6.25 cm².
9. The clostridial neurotoxin for use in a treatment according to claim 7 or 8, or the method according to claim 7 or 8, wherein in step (ii), ultrasound is applied

in one or more lines in each of said one or more areas, in particular in between 5 and 30 lines.

10. The clostridial neurotoxin for use in a treatment according to any one of claims 7 to 9, or the method according to any one of claims 7 to 9, wherein in step (ii), ultrasound is applied at a frequency between 3 and 12 MHz, particularly between 4 and 10 MHz, particularly selected from 4, 7 and 10 MHz.
11. The clostridial neurotoxin for use in a treatment according to any one of claims 7 to 10, or the method according to any one of claims 7 to 10, wherein in step (ii), ultrasound is applied with a focal depth of between 1 and 5 mm, particularly between 1.5 and 4.5 mm, particularly selected from 1.5 mm, 3 mm and 4.5 mm.
12. The clostridial neurotoxin for use in a treatment according to claim 11, or the method according to claim 11, said lines are applied by using the set of conditions as shown in Table 2, part B.
13. The clostridial neurotoxin for use in a treatment according to any one of claims 3 to 12, or the method according to any one of claims 3 to 12,
wherein the cylindrical transduction element comprises a first surface and a second surface,
wherein the first surface comprises an electrically conductive coating,
wherein the second surface comprises at least one electrically conductive coated region and at least one region that is not coated with an electrically conductive coating,
wherein the at least one coated region on the second surface comprises a conductive material that forms an electrode when the power source is in electric communication with the at least one coated region,

wherein the at least one coated region on the second surface is configured to reduce edge noise at the linear focal zone at the focal depth.

14. The clostridial neurotoxin for use in a treatment according to any one of claims 3 to 13, or the method according to any one of claims 3 to 13, further comprising one or more imaging elements, wherein the cylindrical transduction element has an opening configured for placement of the one or more imaging elements,

wherein the cylindrical transduction element is housed within an ultrasonic hand-held probe, wherein the ultrasonic probe comprises:

a housing,

the cylindrical transduction element, and

a motion mechanism;

wherein the ultrasound transducer is movable within the housing,

wherein the motion mechanism is attached to the ultrasound transducer and configured to move the ultrasound transducer along a linear path within the housing.

wherein the conductive material is silver,

wherein the first surface is a concave surface and the second surface is a convex surface.

15. The clostridial neurotoxin for use in a treatment according to any one of claims 3 to 14, or the method according to any one of claims 3 to 14, wherein the cylindrical transduction element is housed within an ultrasonic hand-held probe, wherein the ultrasonic probe comprises:

a housing,

the cylindrical transduction element, and

a motion mechanism;

wherein the ultrasound transducer is movable within the housing,
wherein the motion mechanism is attached to the ultrasound transducer
and configured to move the ultrasound transducer along a linear path
within the housing.

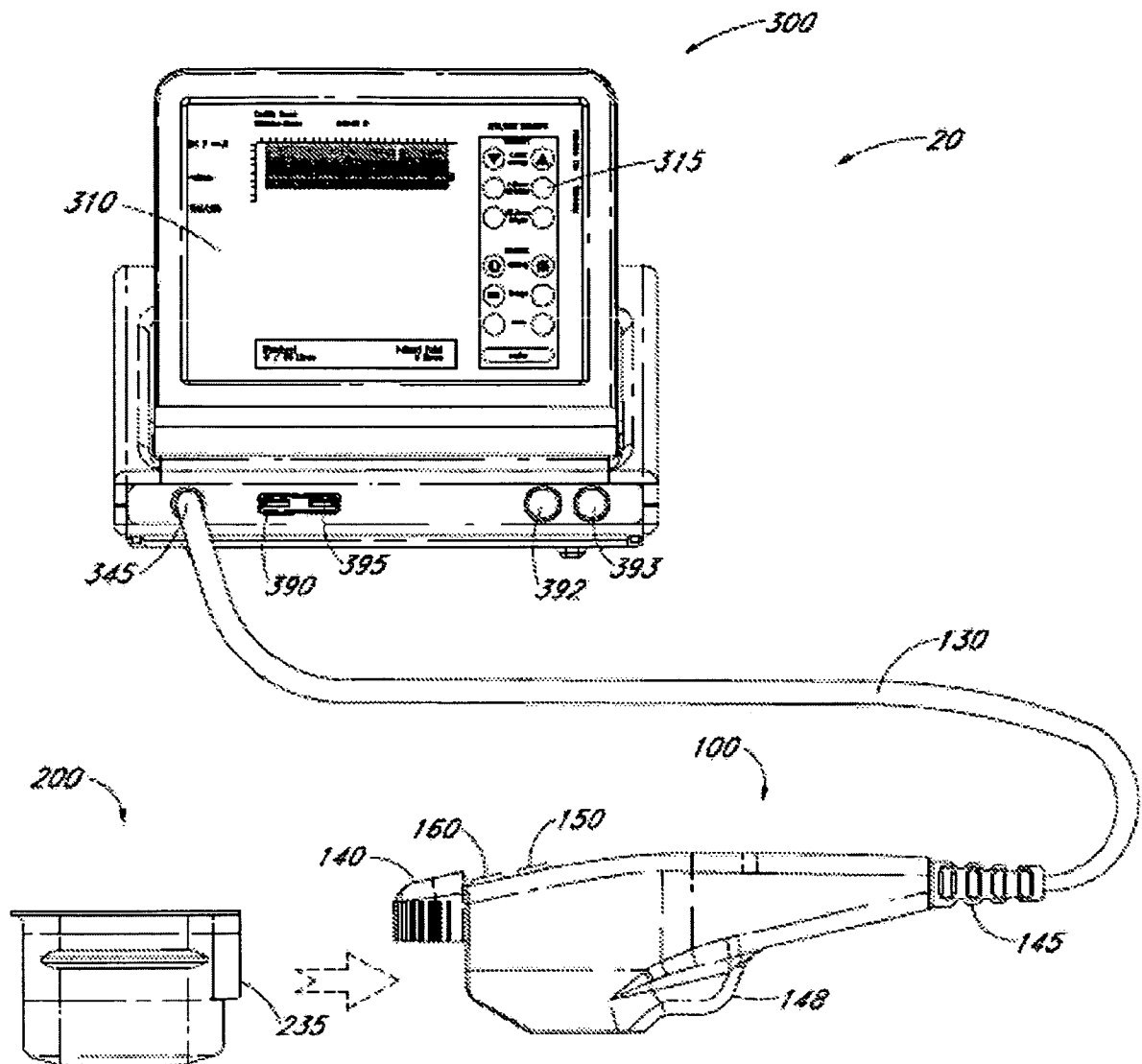


FIG. 1

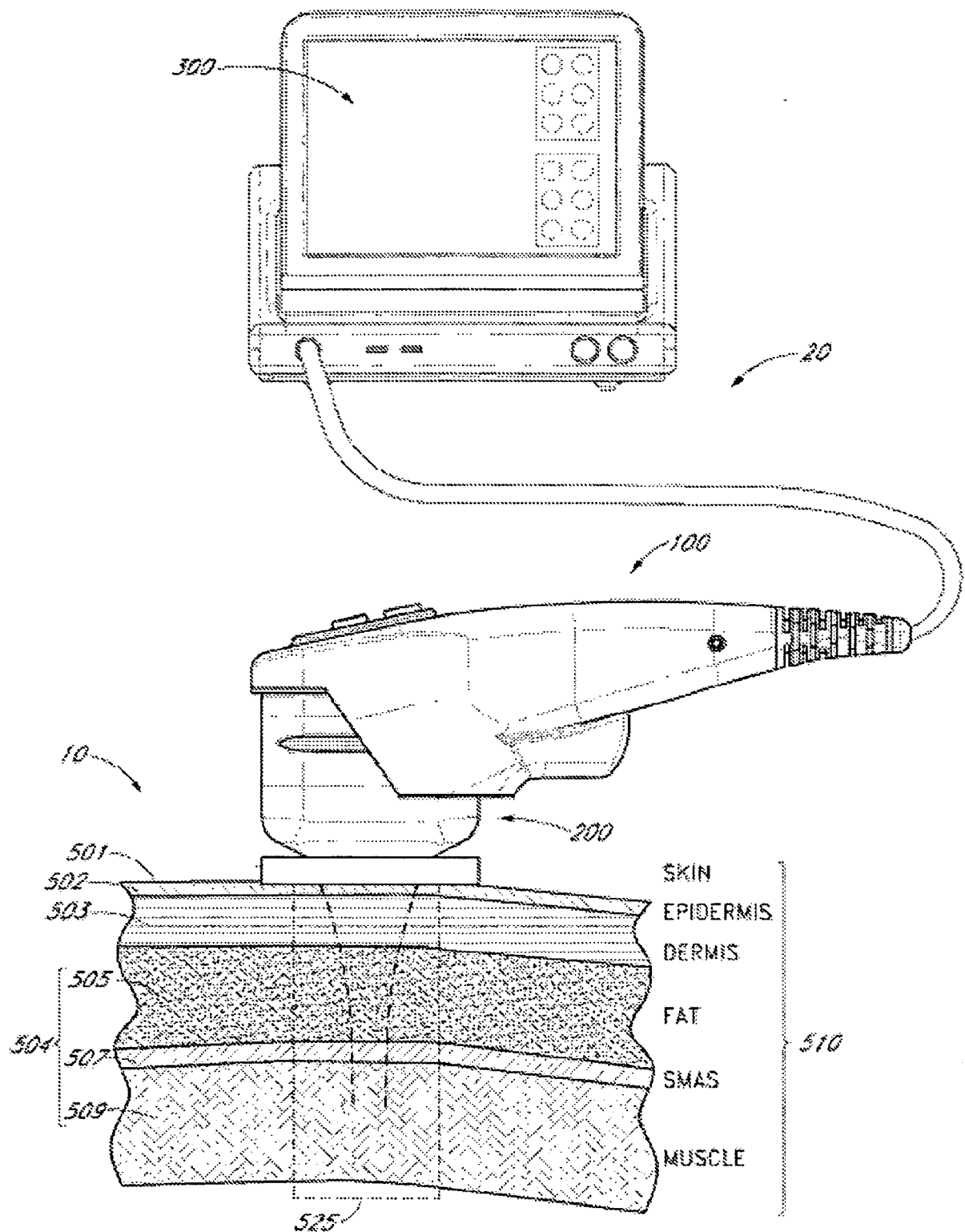
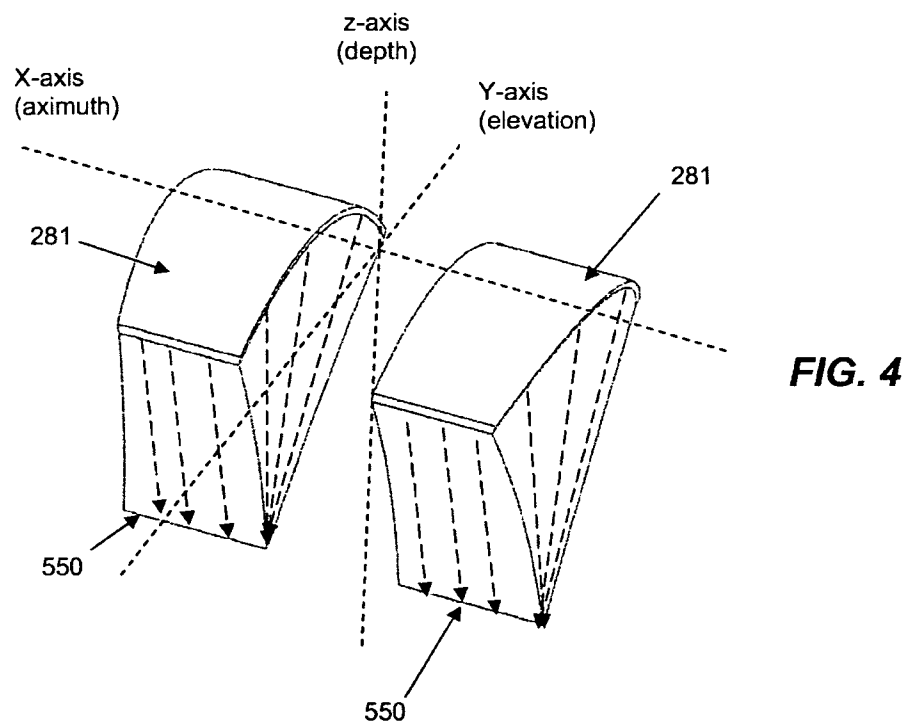
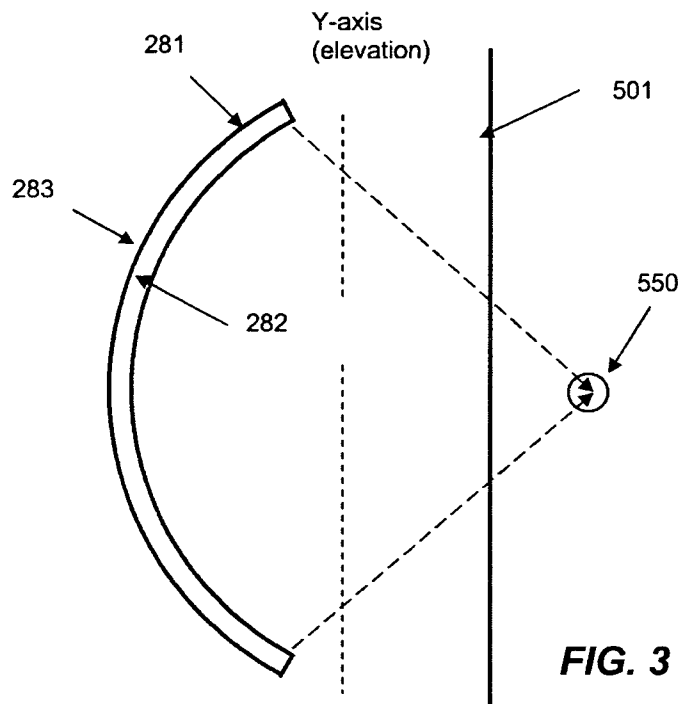


FIG. 2



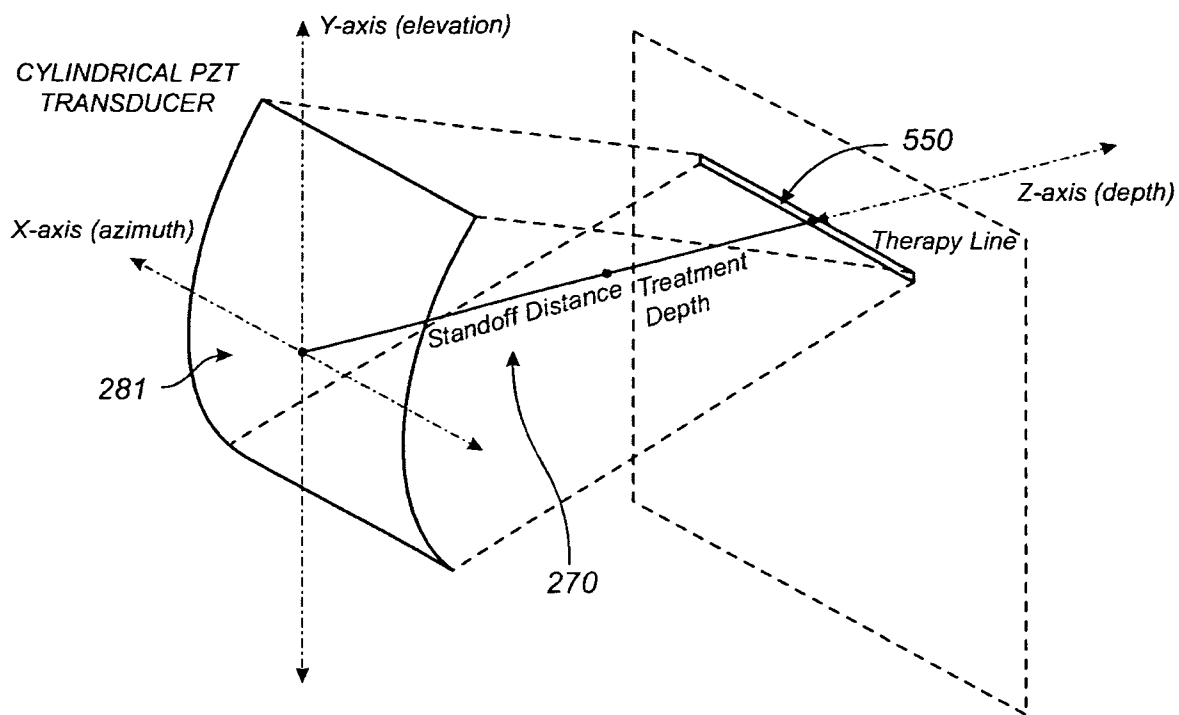


FIG. 5A

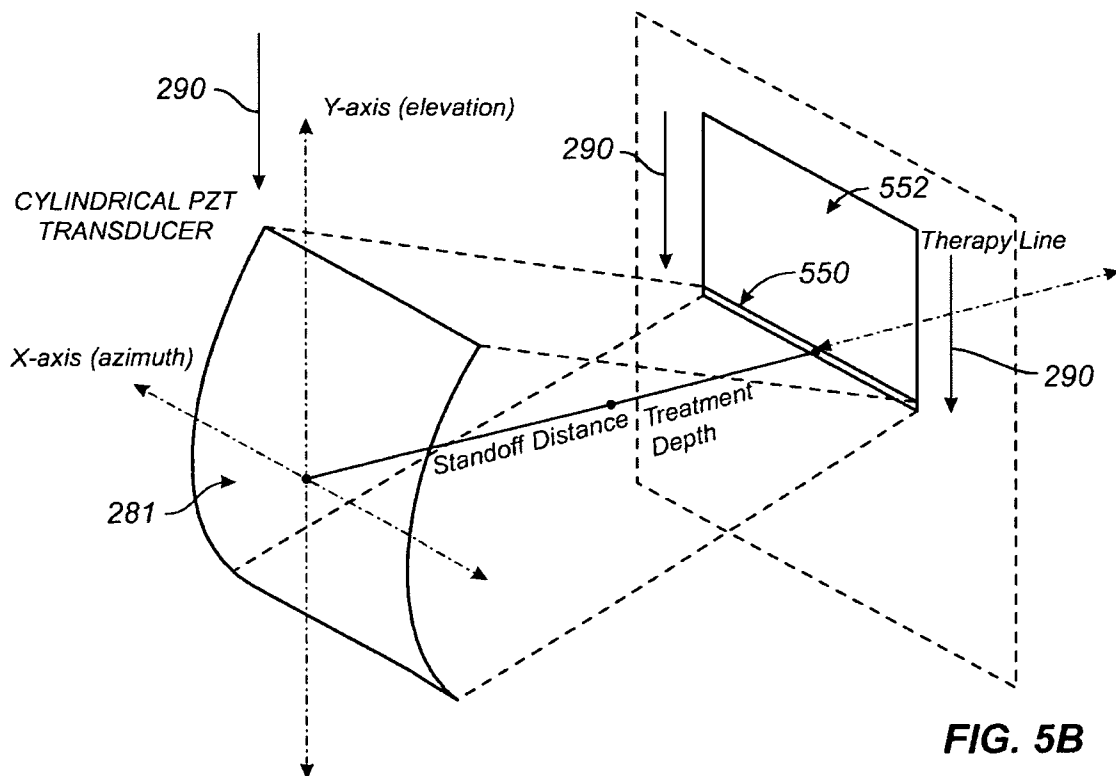


FIG. 5B

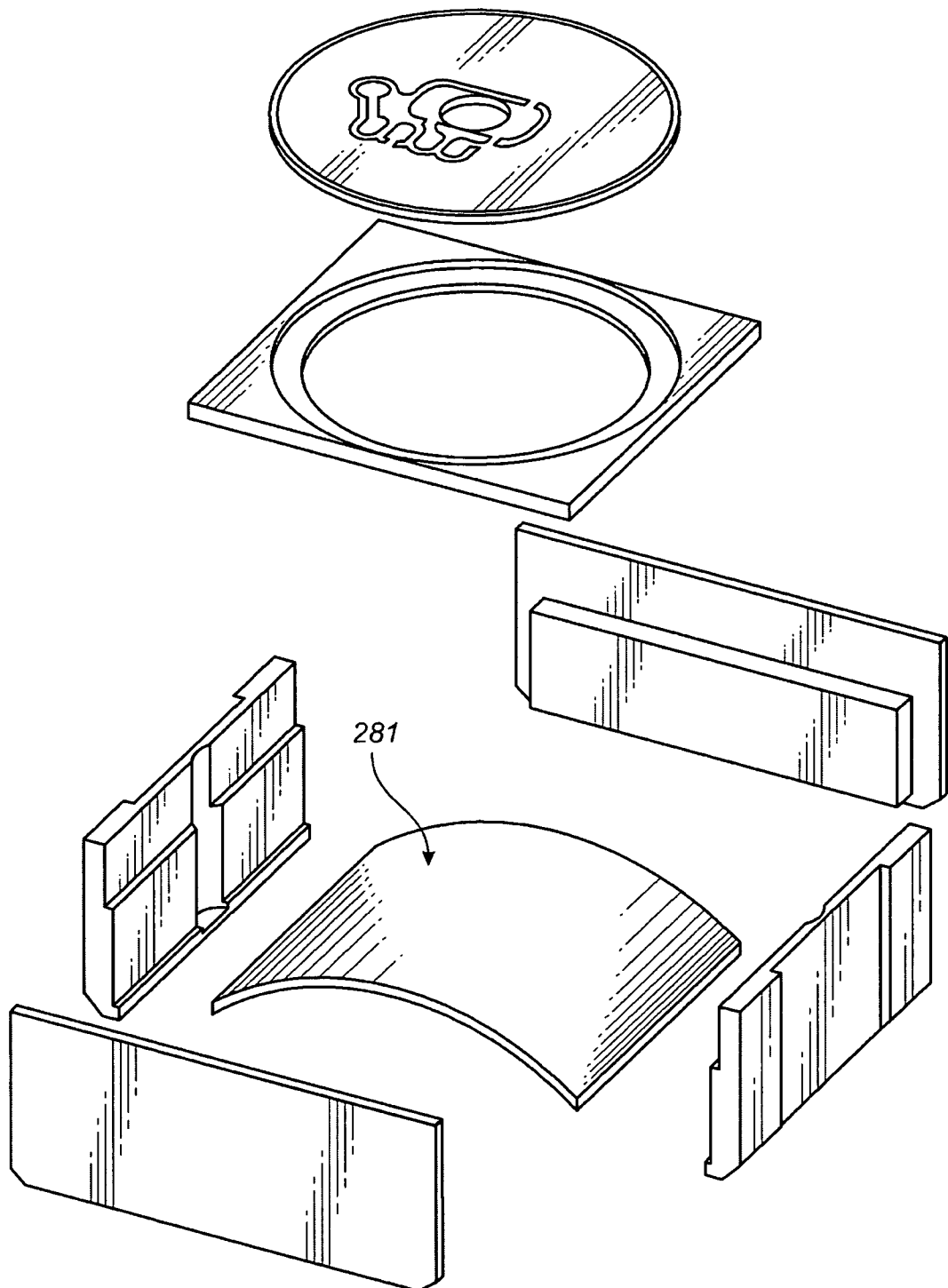


FIG. 6

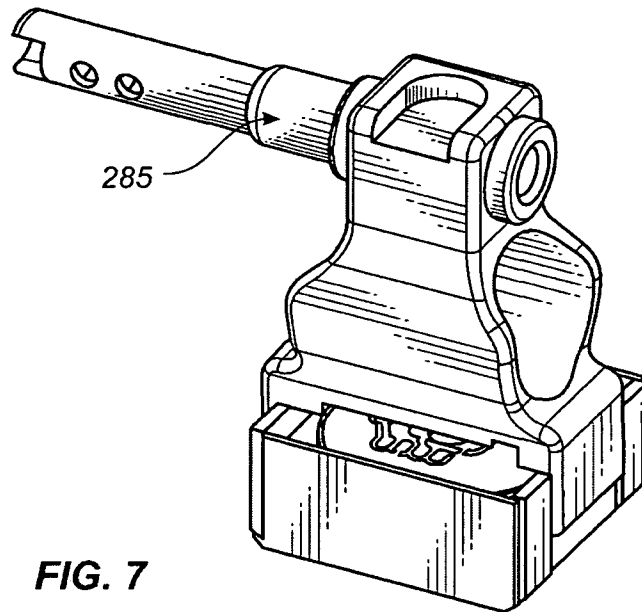


FIG. 7

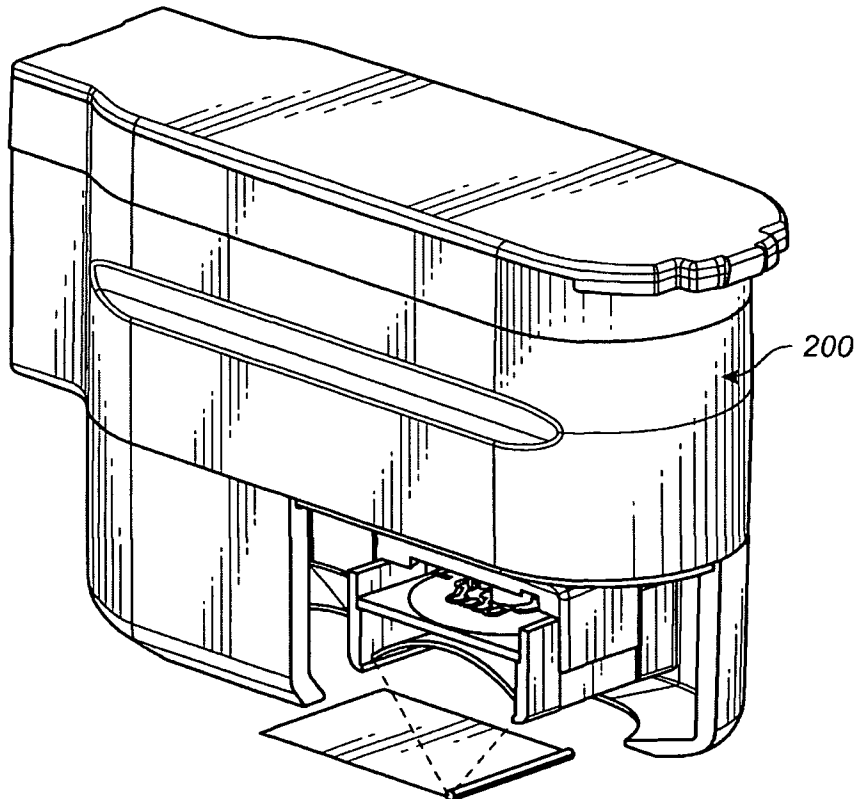
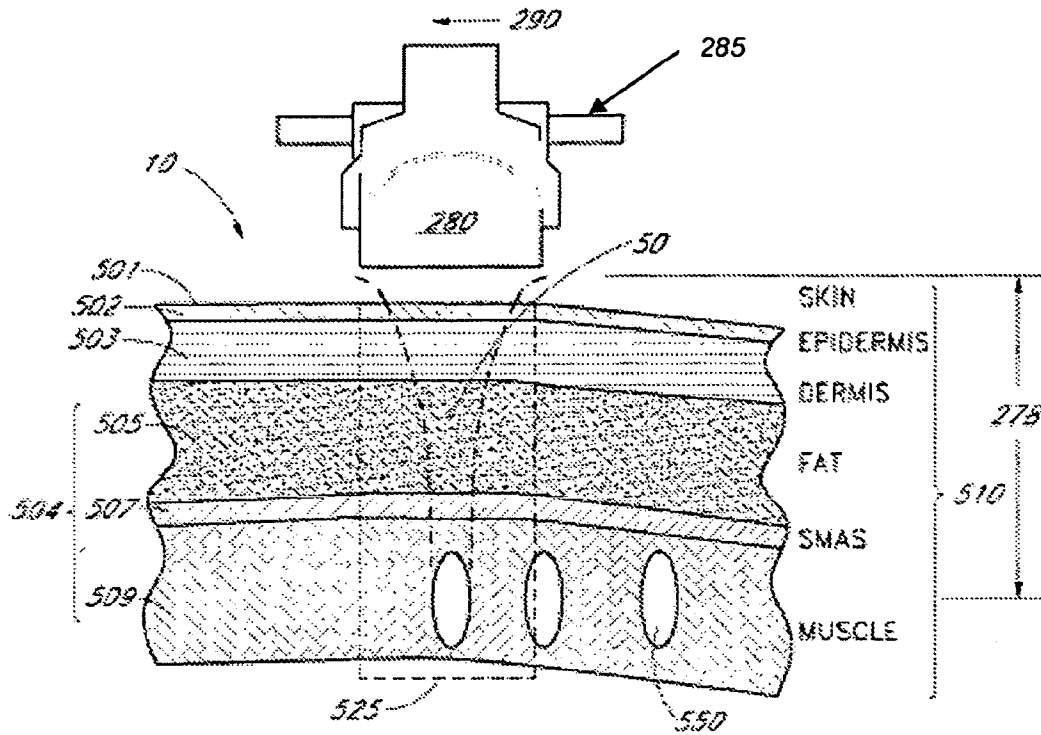
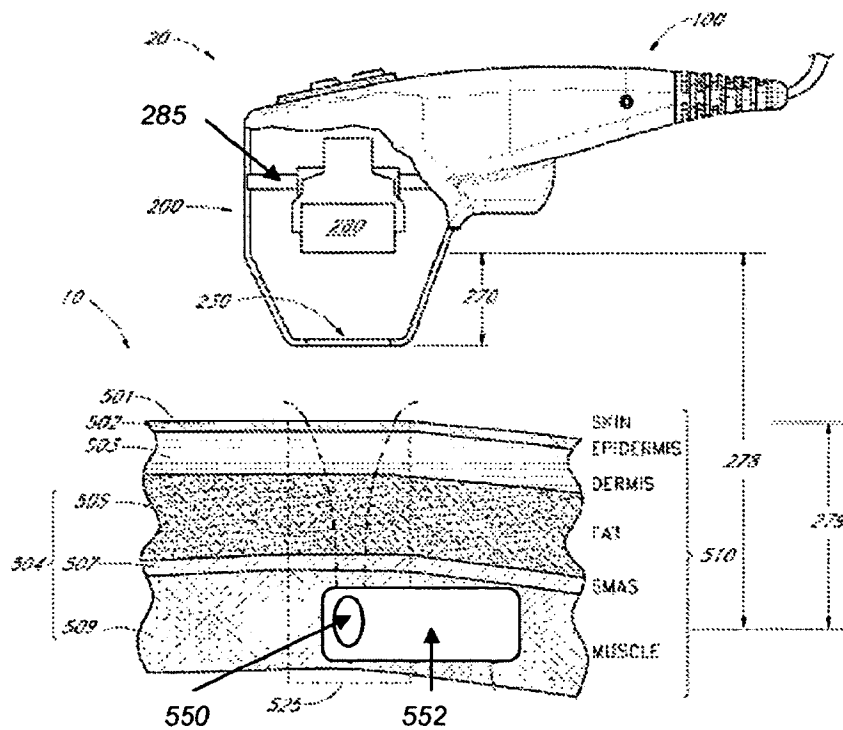
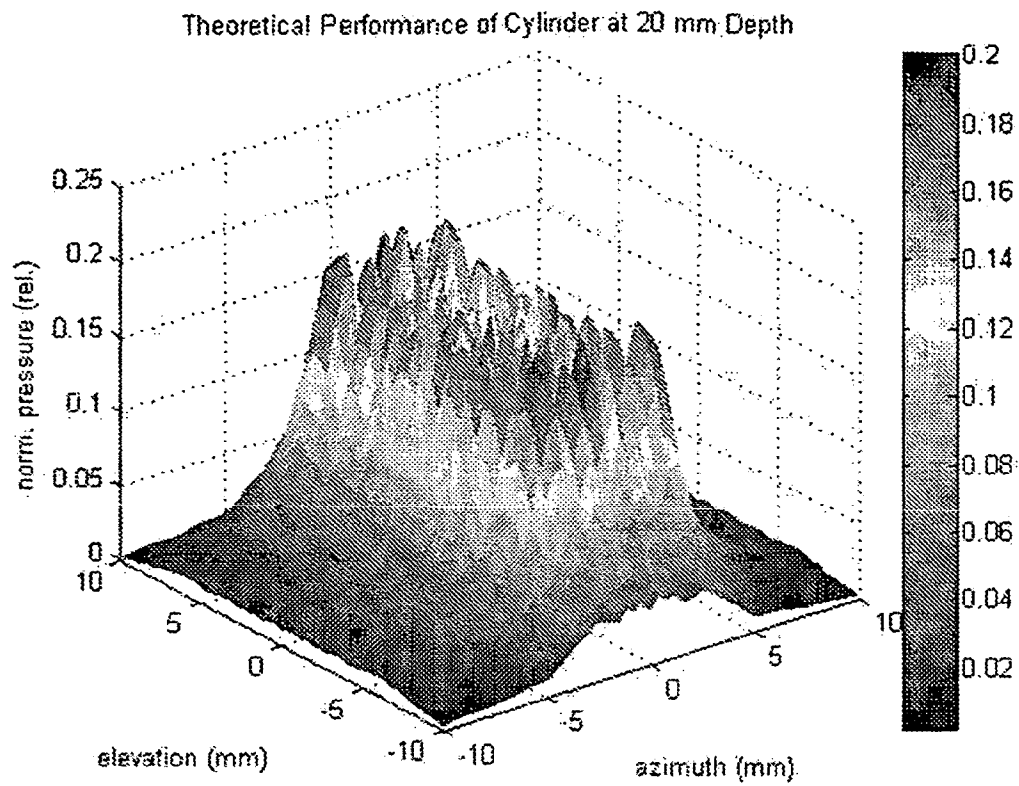
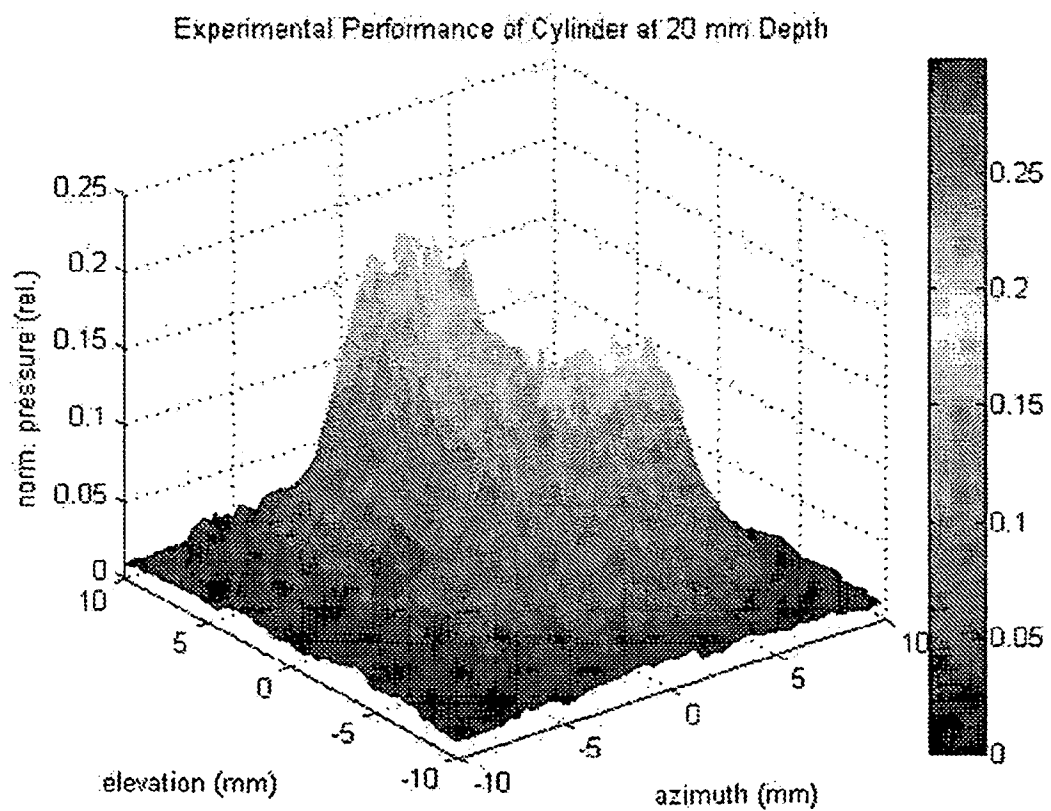
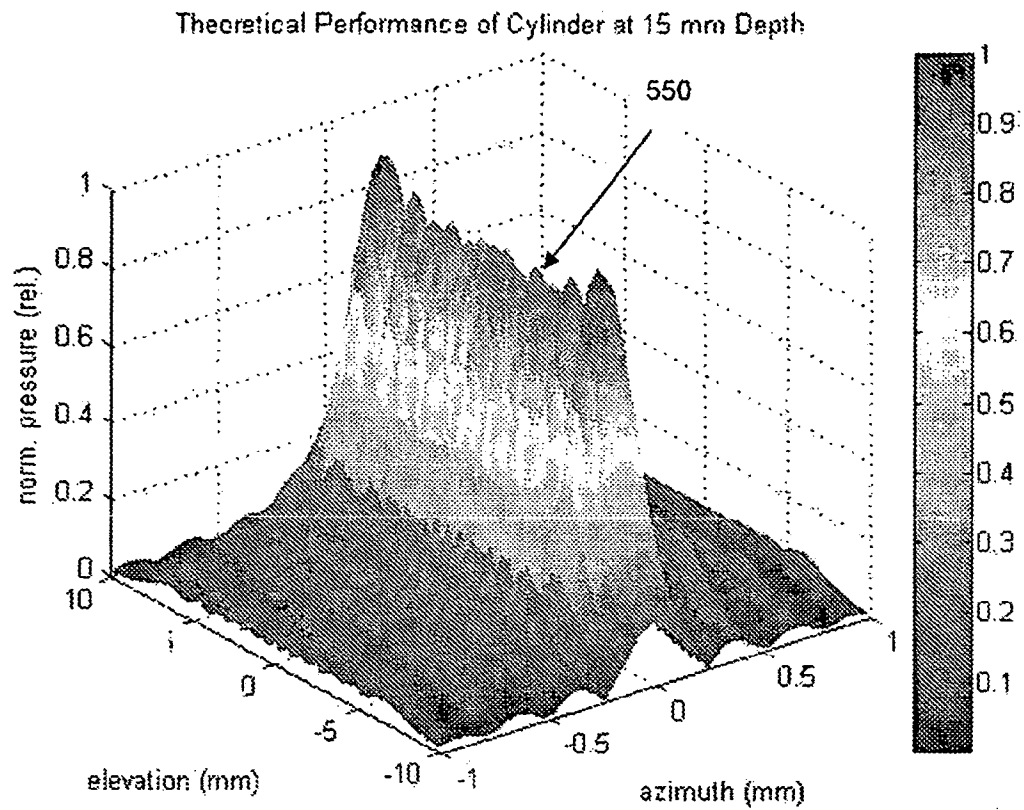
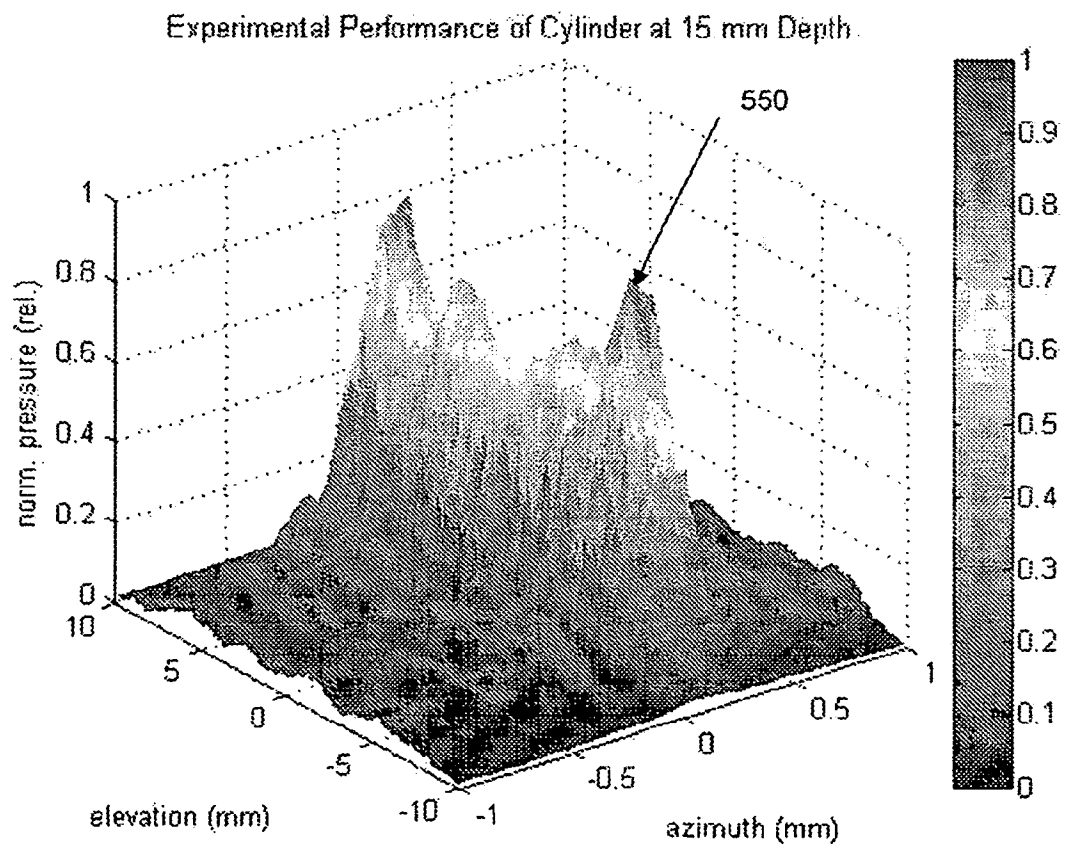


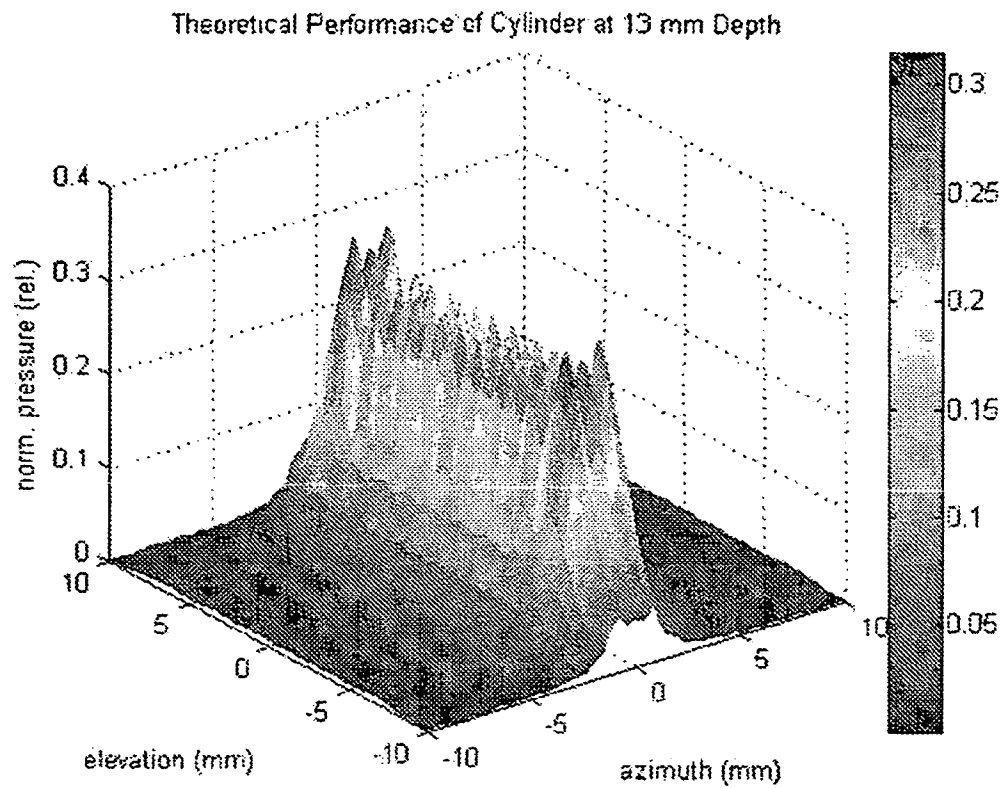
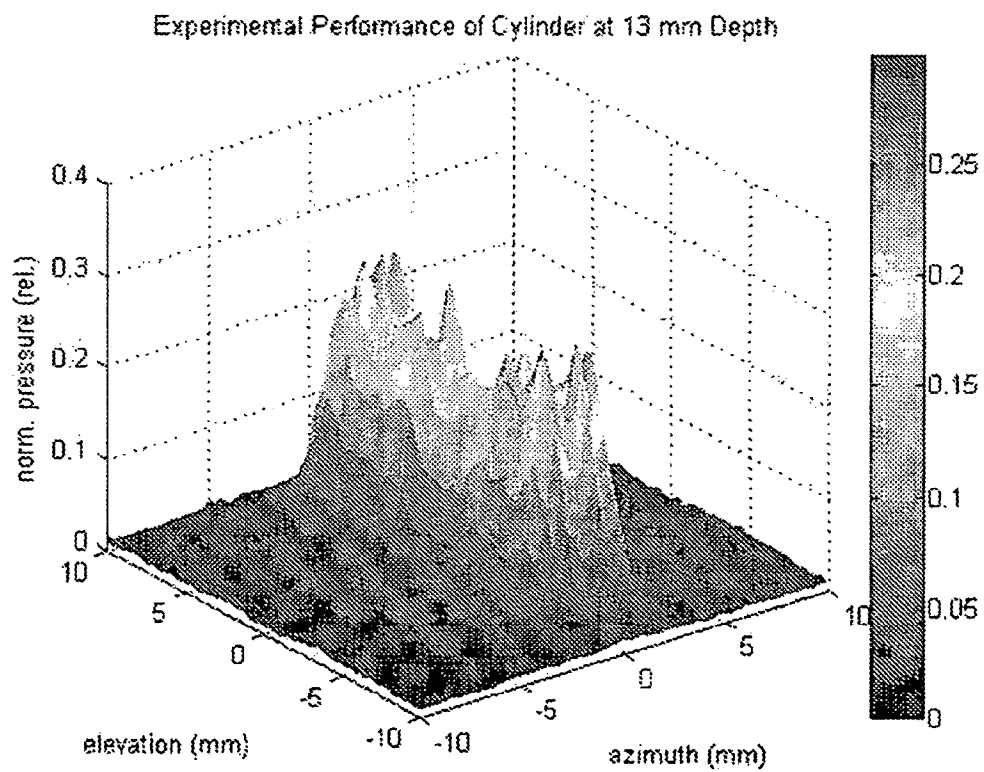
FIG. 8

7/52

**FIG. 9****FIG. 10**

**FIG. 11A****FIG. 11B**

**FIG. 12A****FIG. 12B**

**FIG. 13A****FIG. 13B**

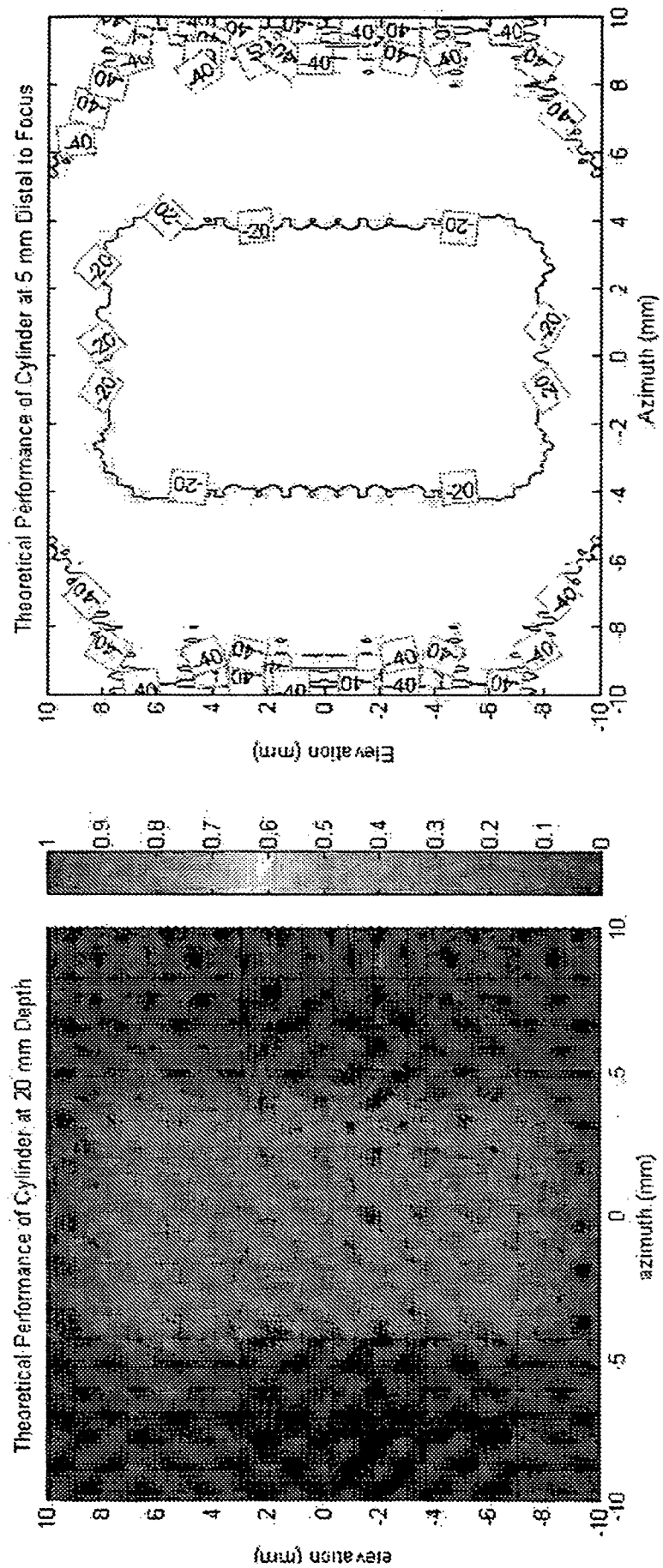


FIG. 14A

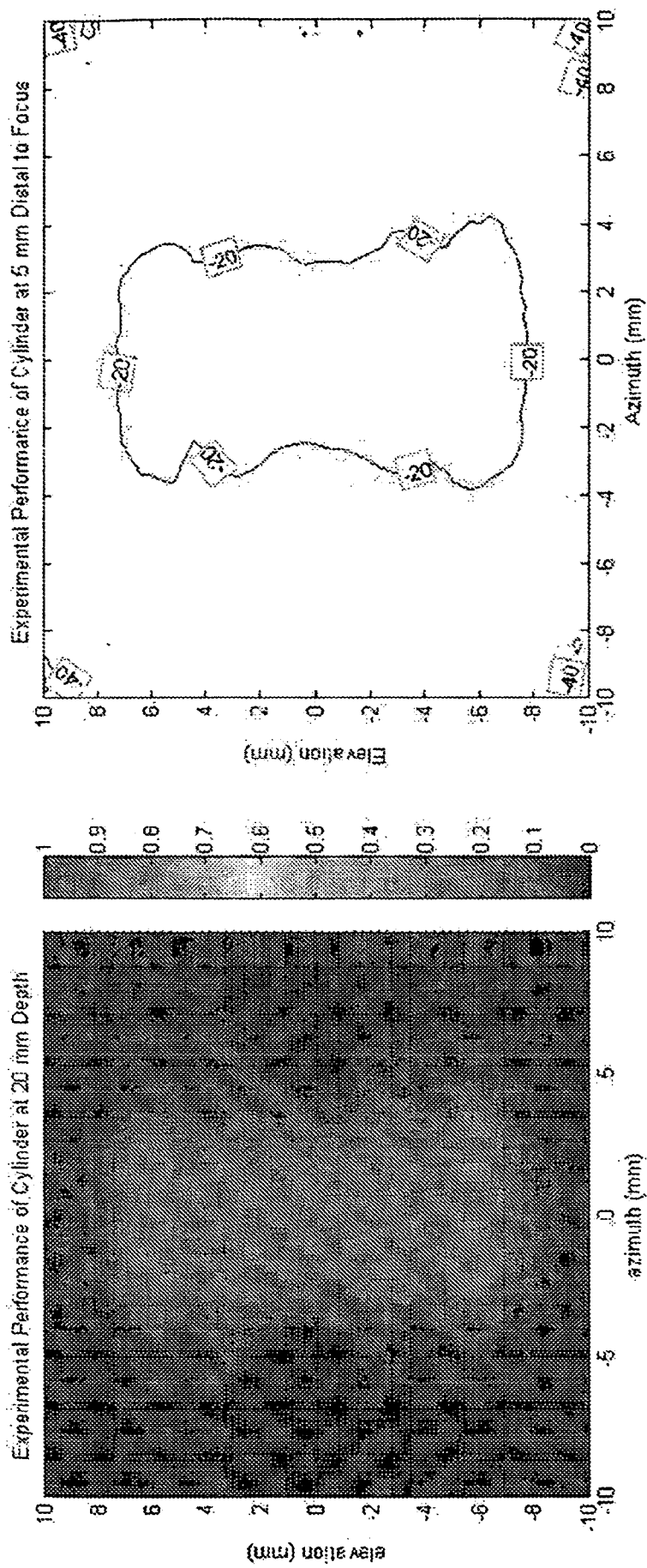


FIG. 14B

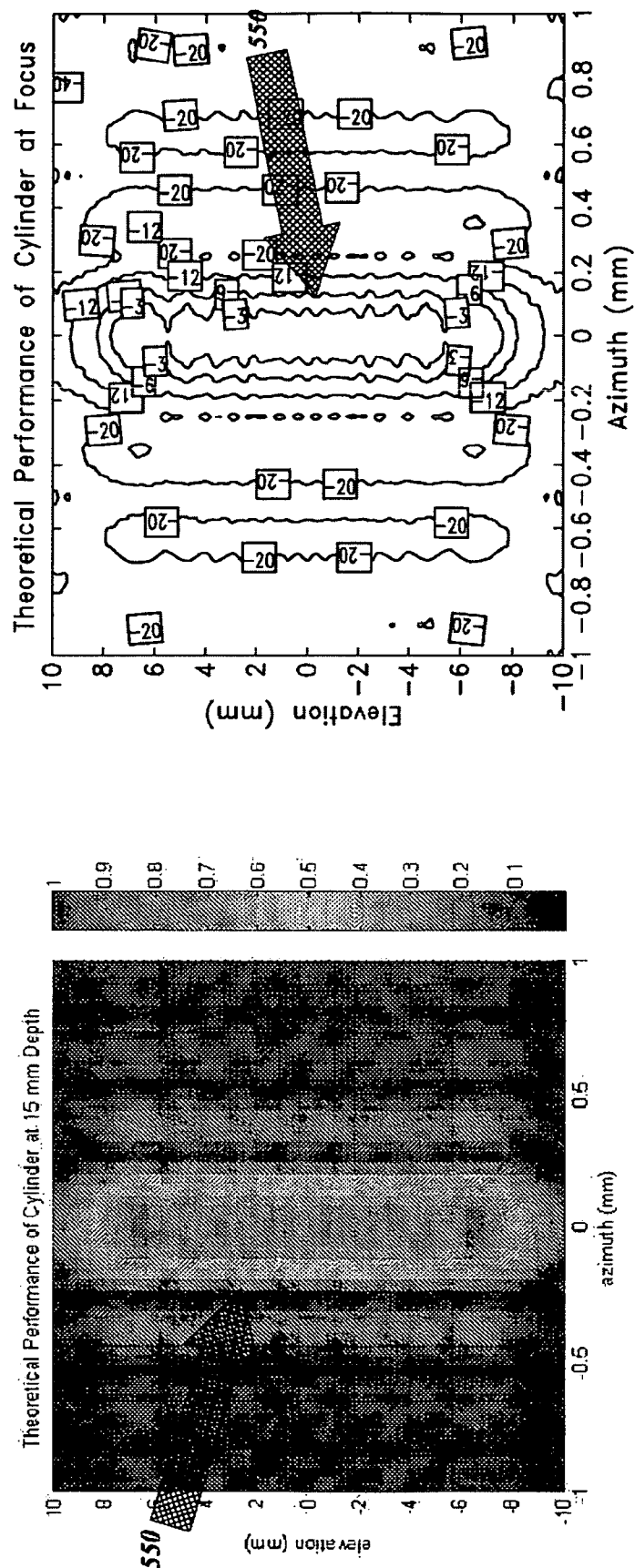


FIG. 15A

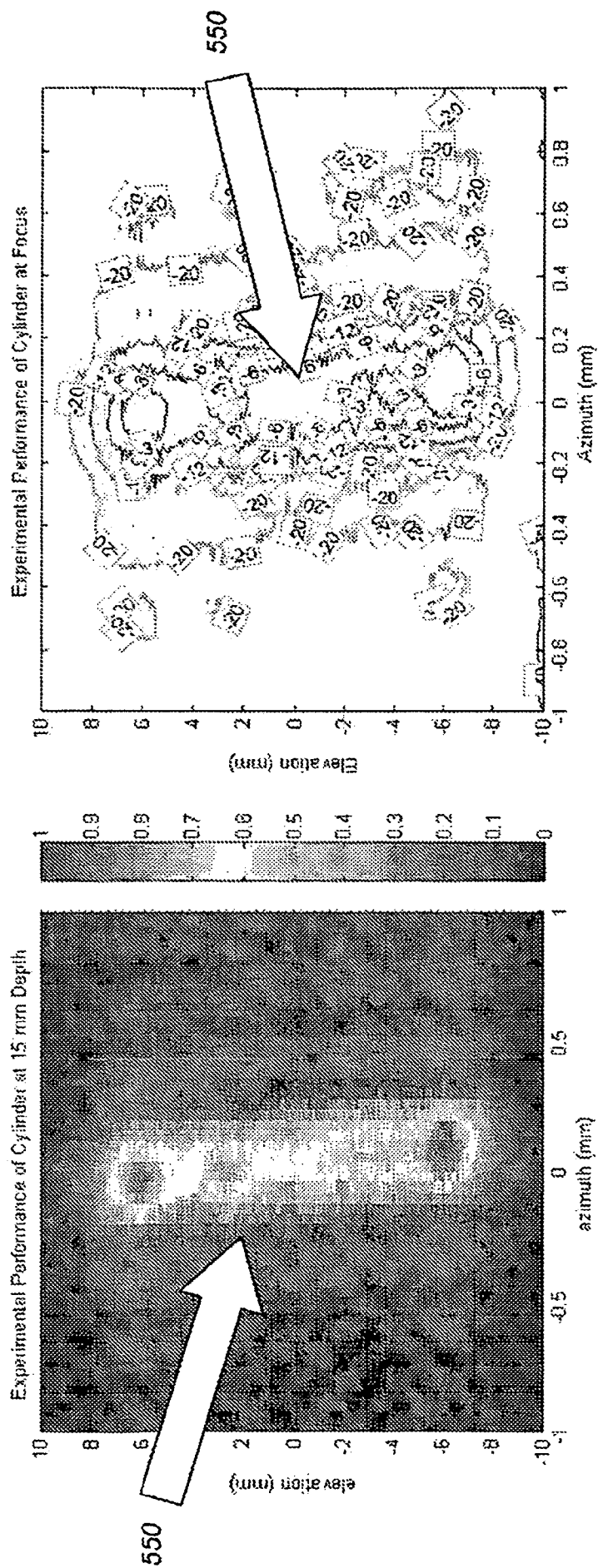


FIG. 15B

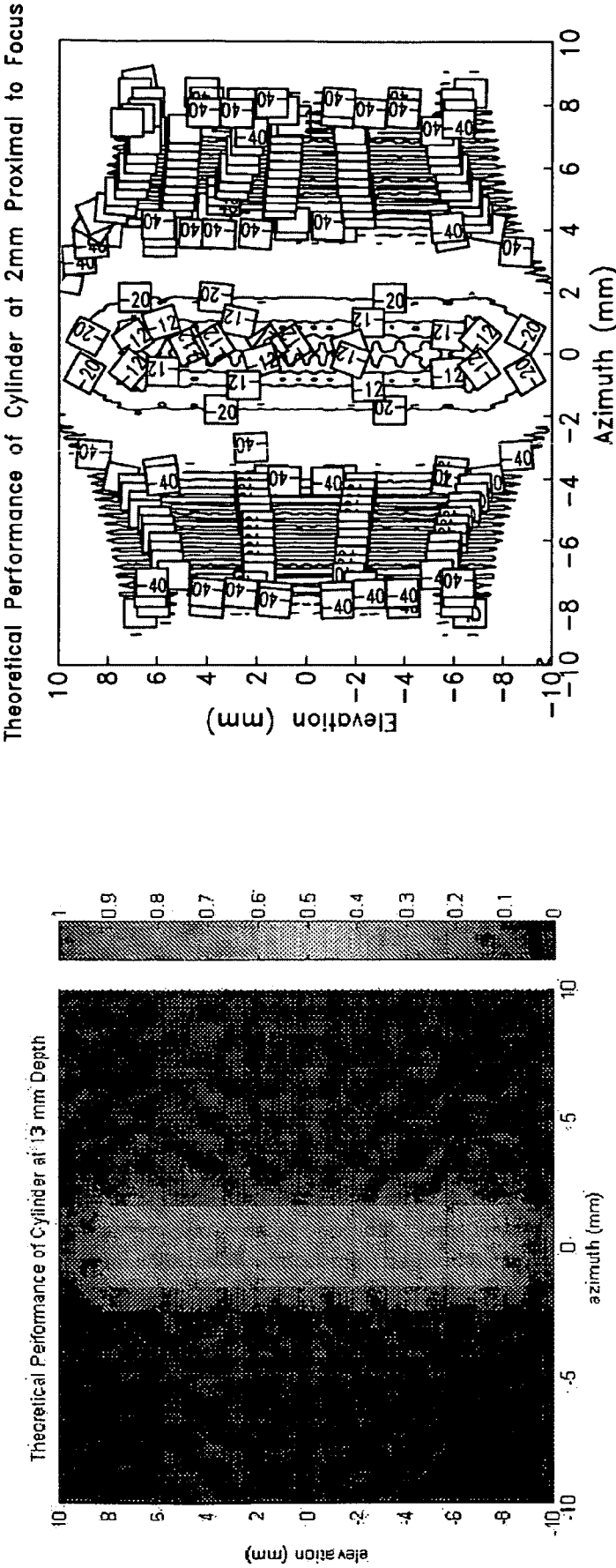


FIG. 16A

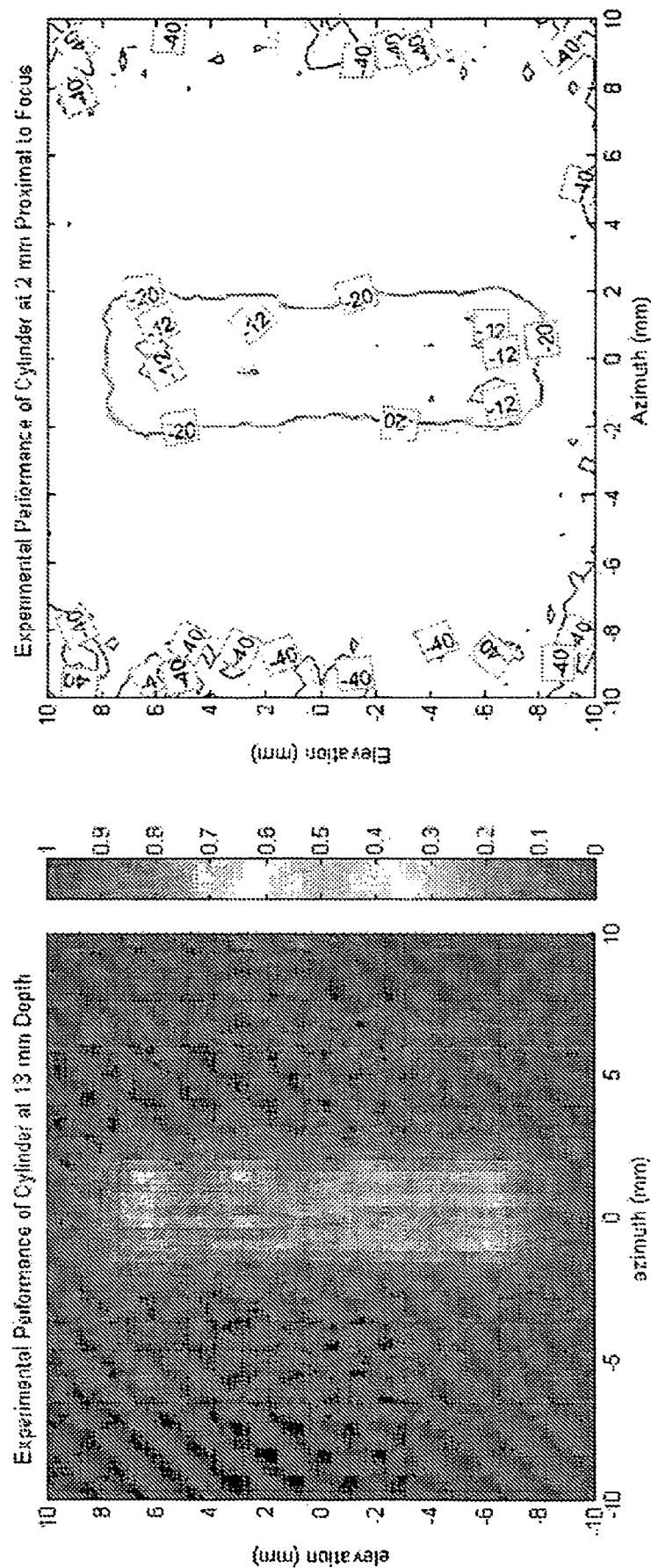
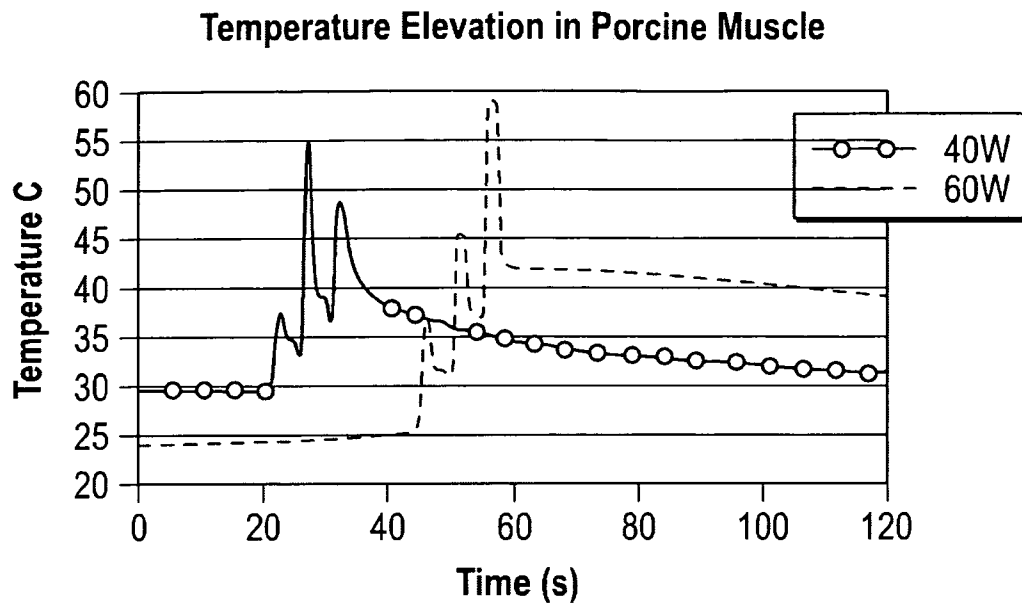
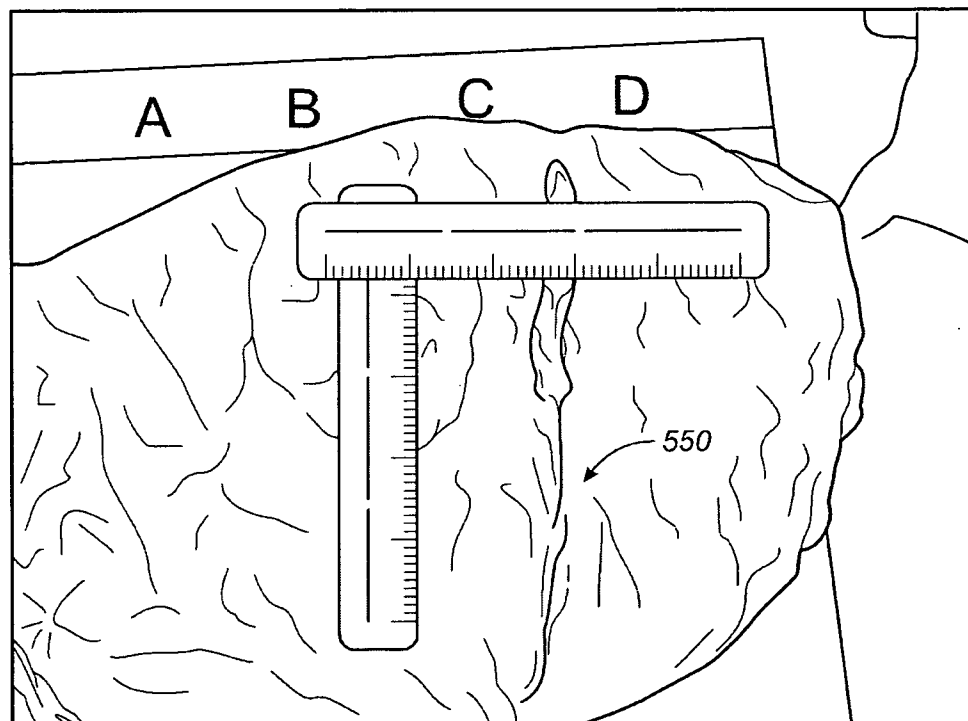


FIG. 16B

**FIG. 17****FIG. 18**

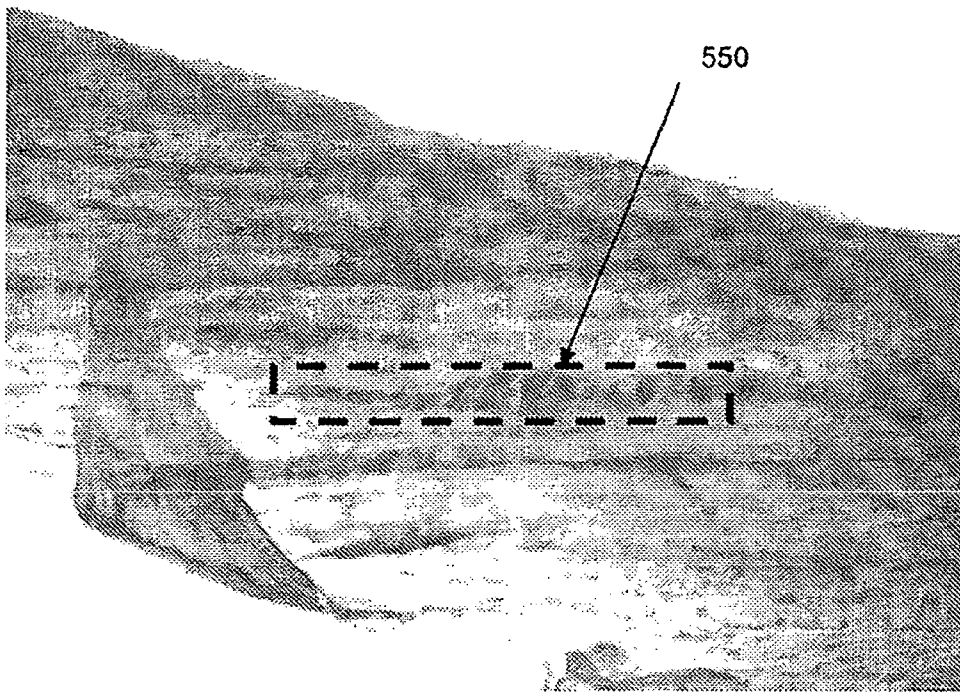


FIG. 19

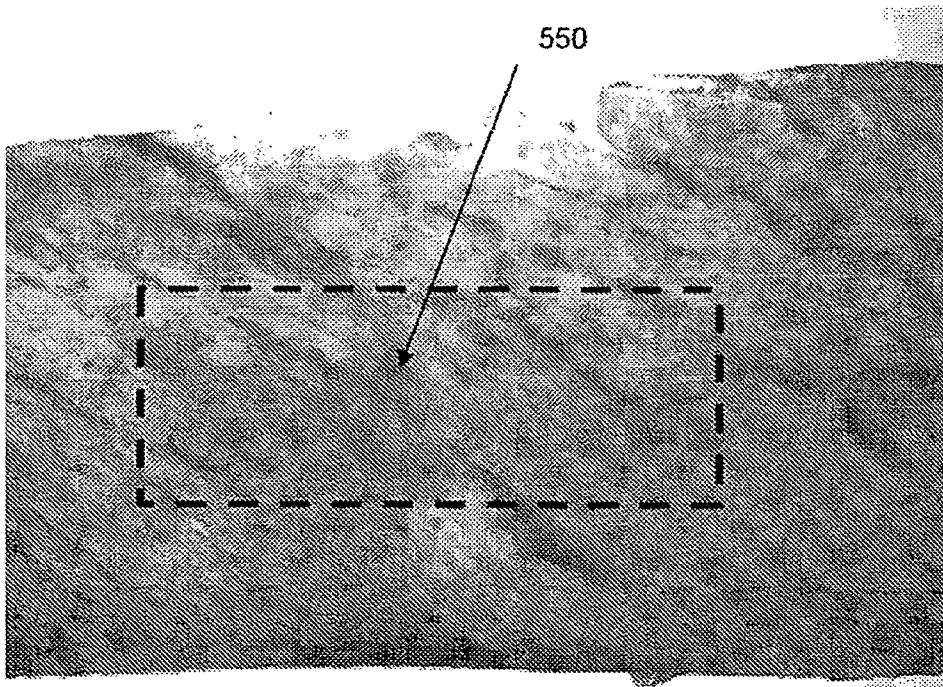


FIG. 20

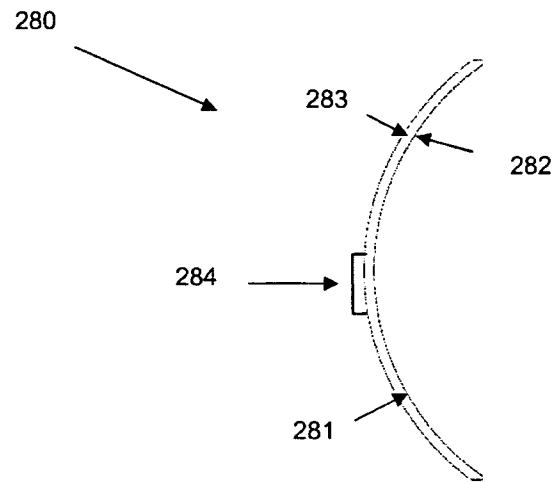


FIG. 21

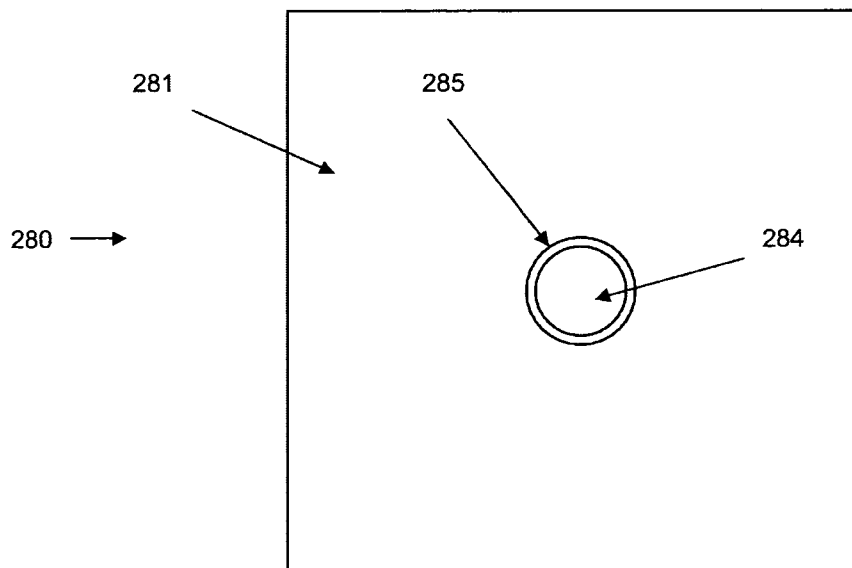
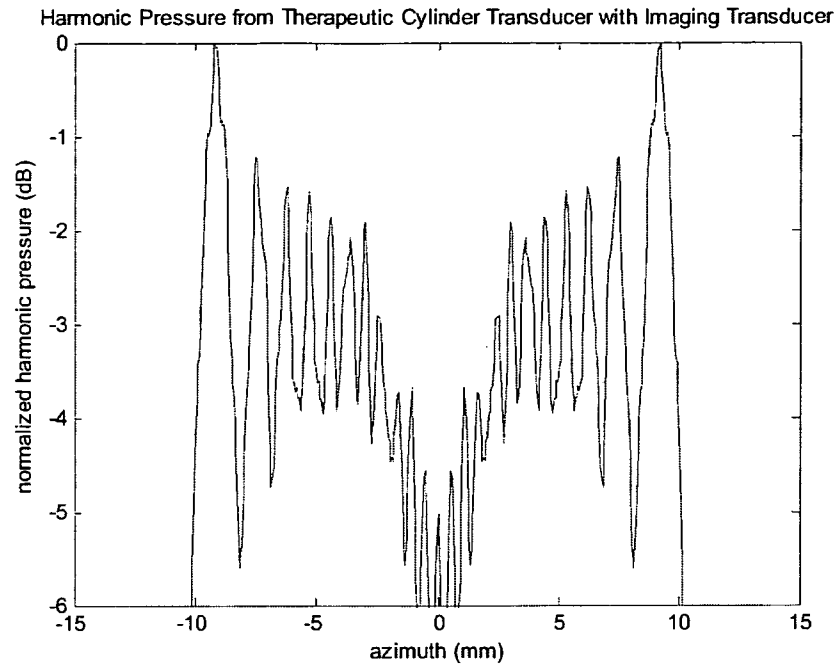
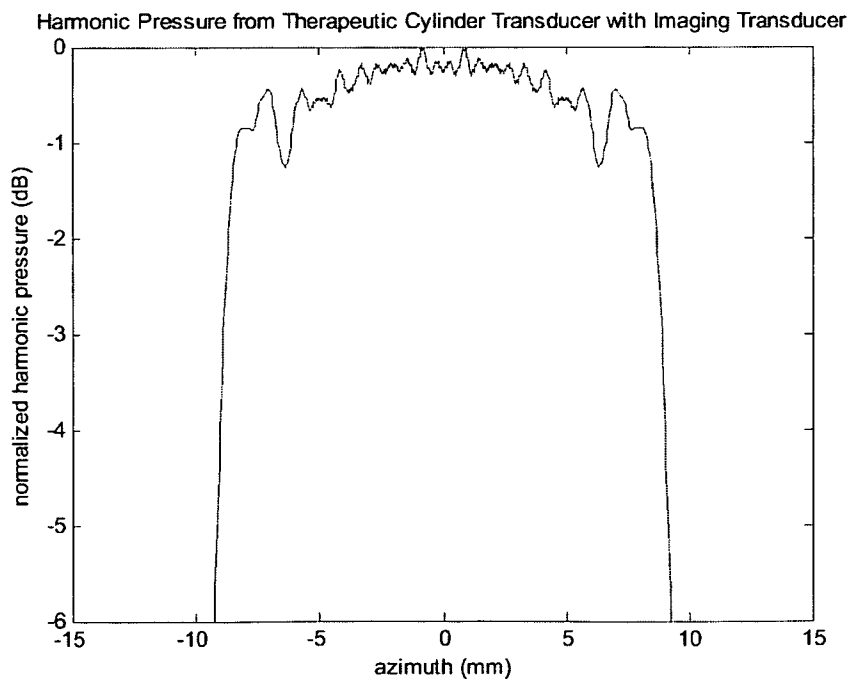
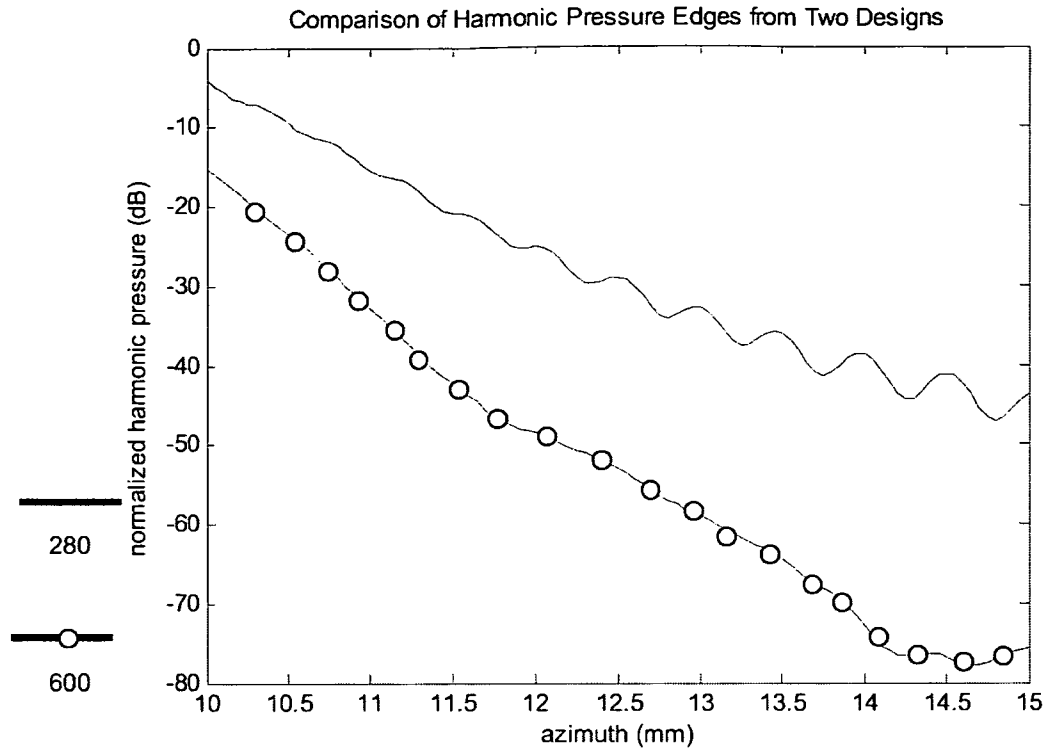


FIG. 22

**FIG. 23****FIG. 24**

**FIG. 25**

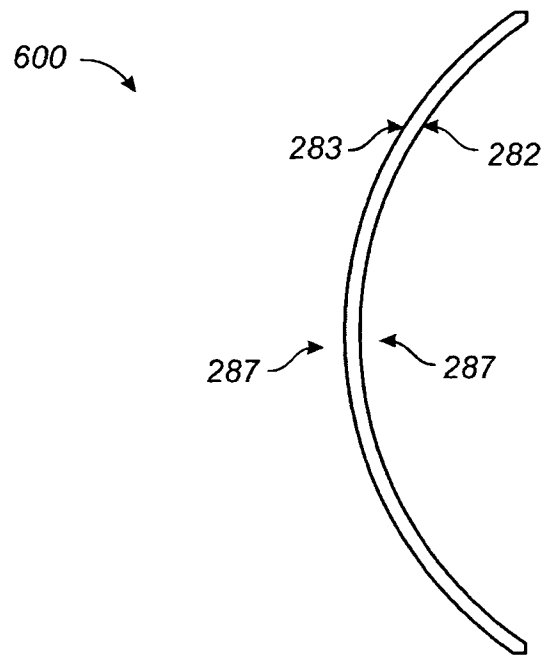


FIG. 26

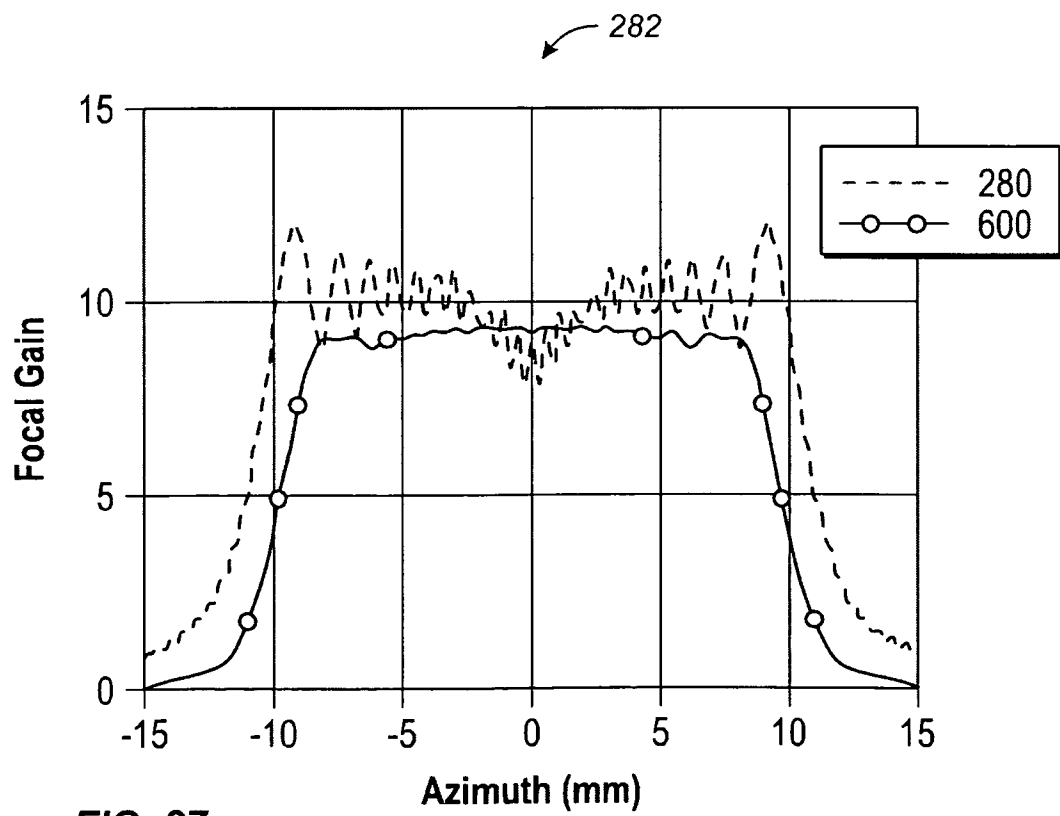
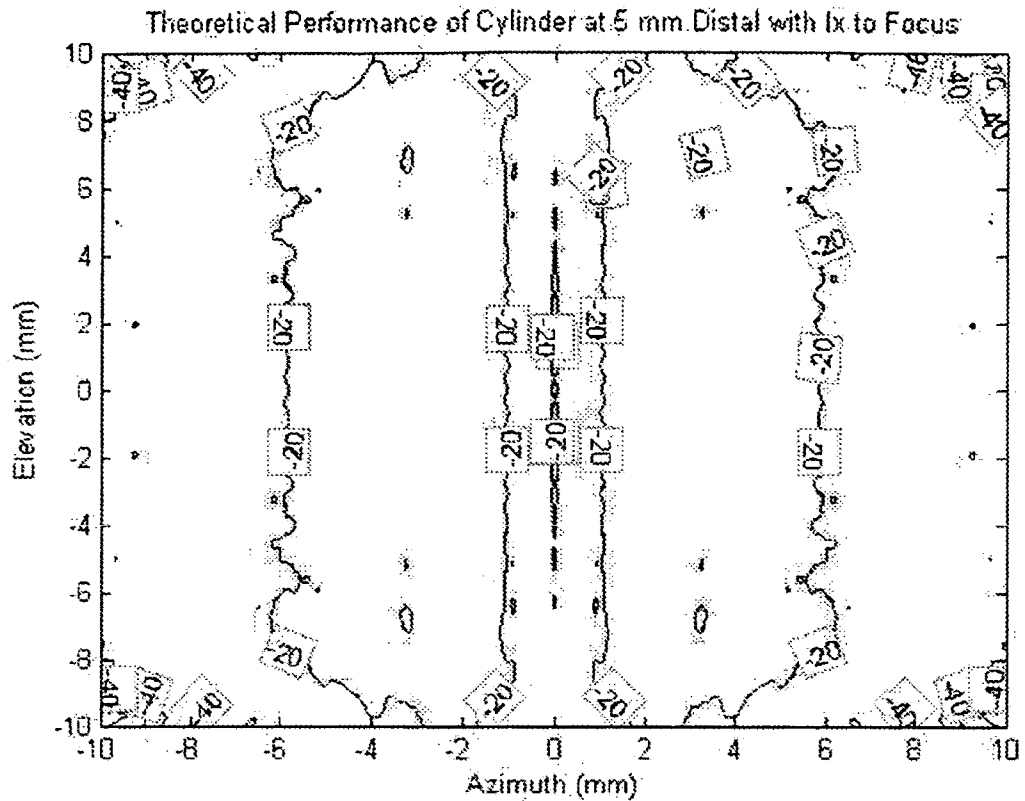
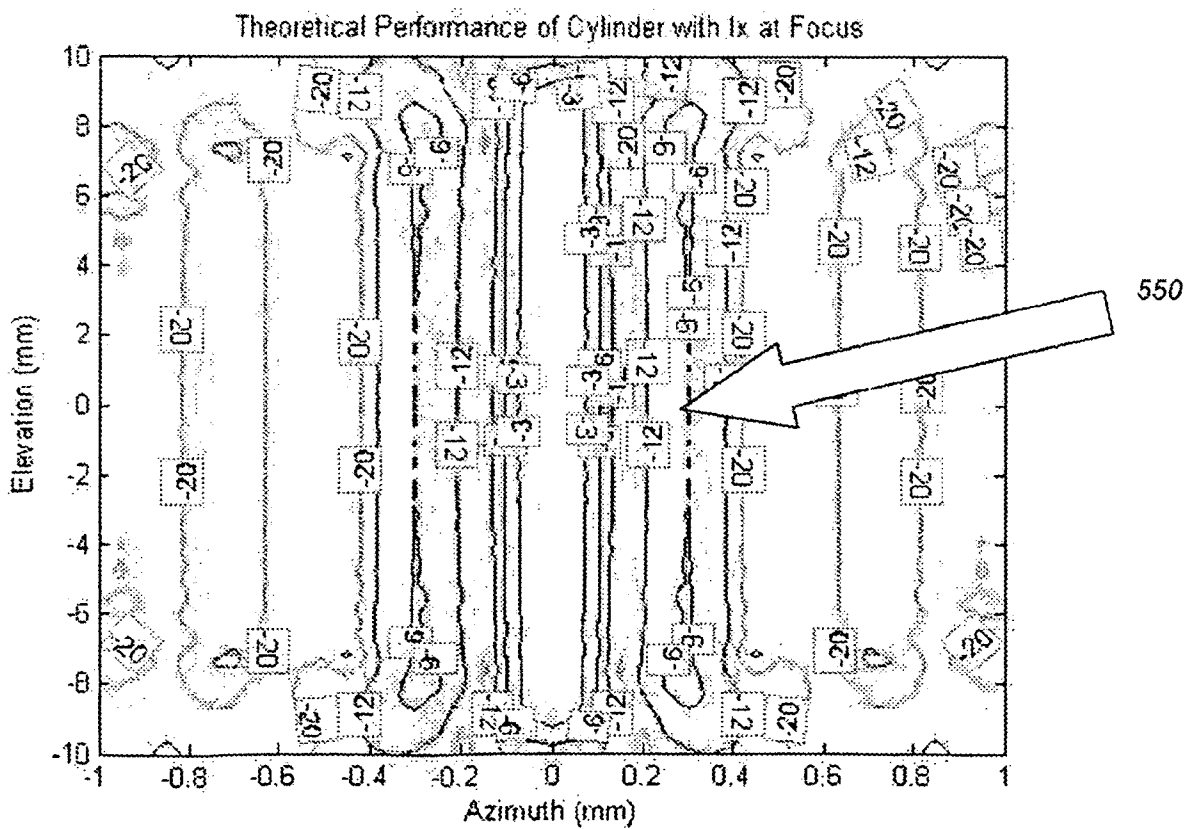


FIG. 27

**FIG. 28****FIG. 29**

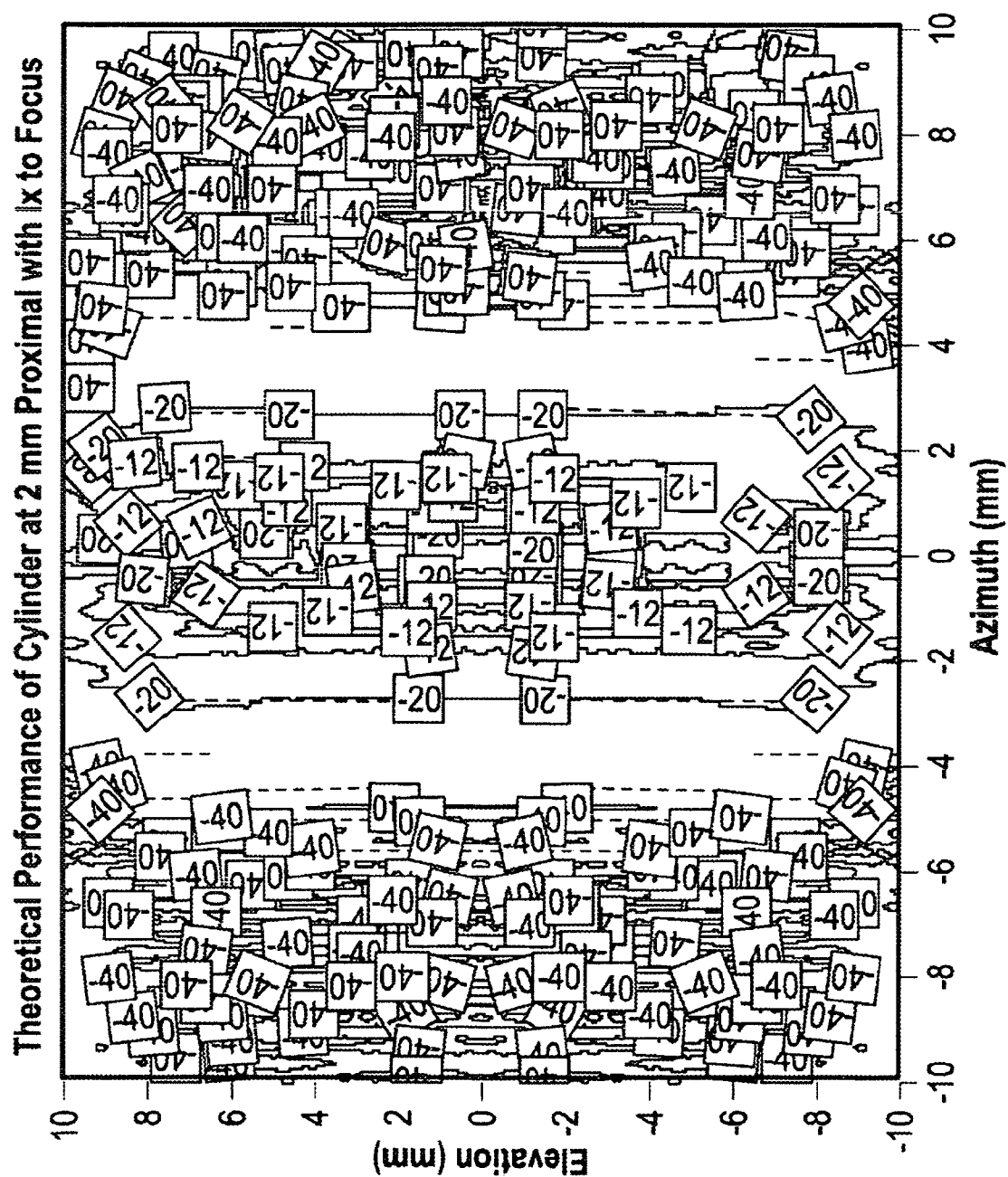


FIG. 30

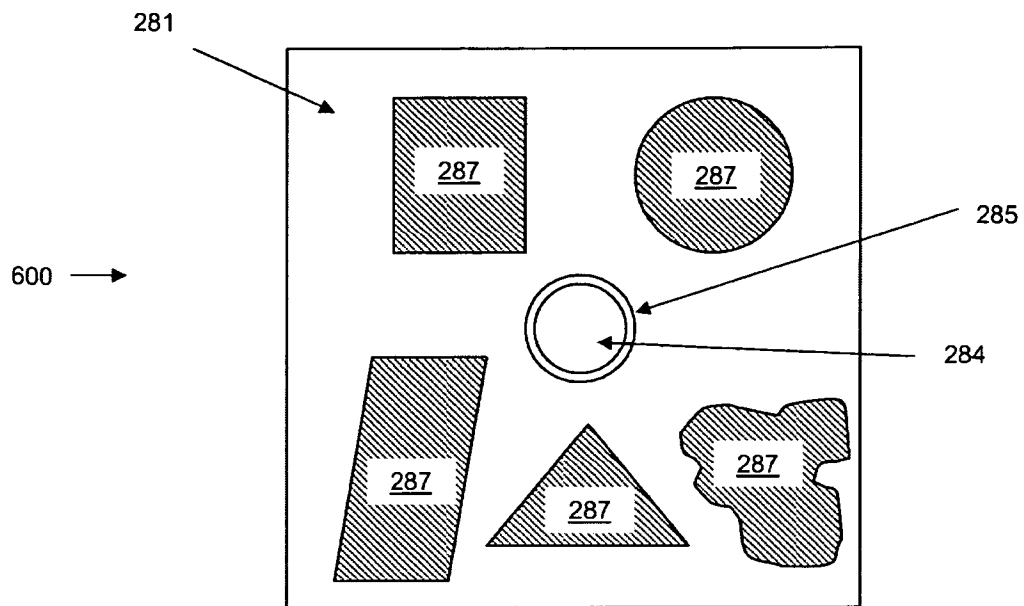


FIG. 31

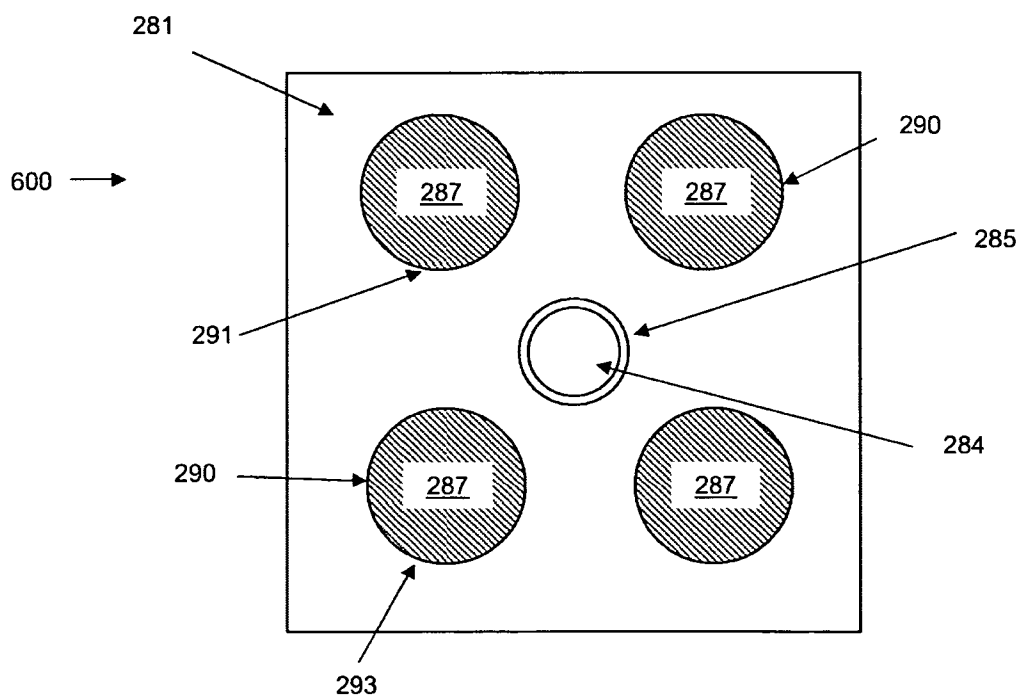
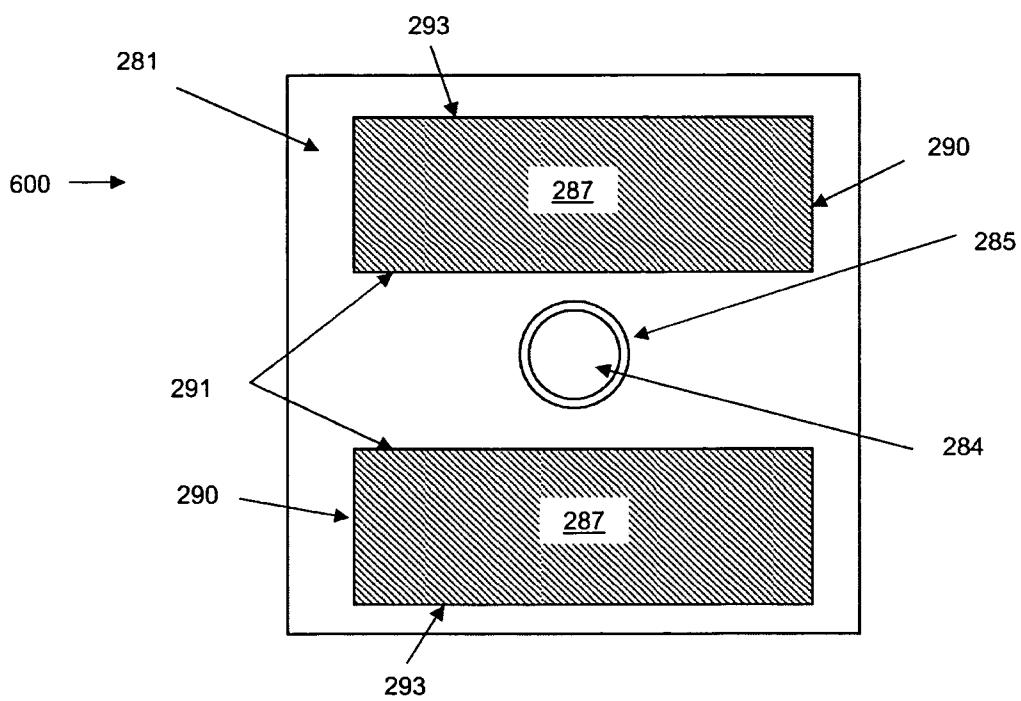
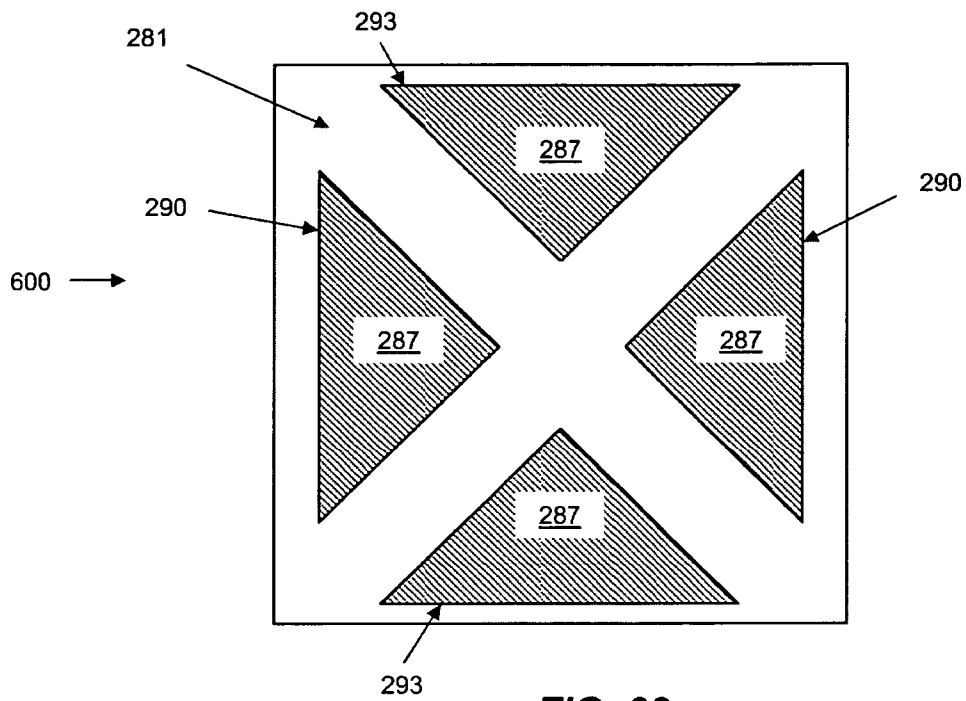


FIG. 32



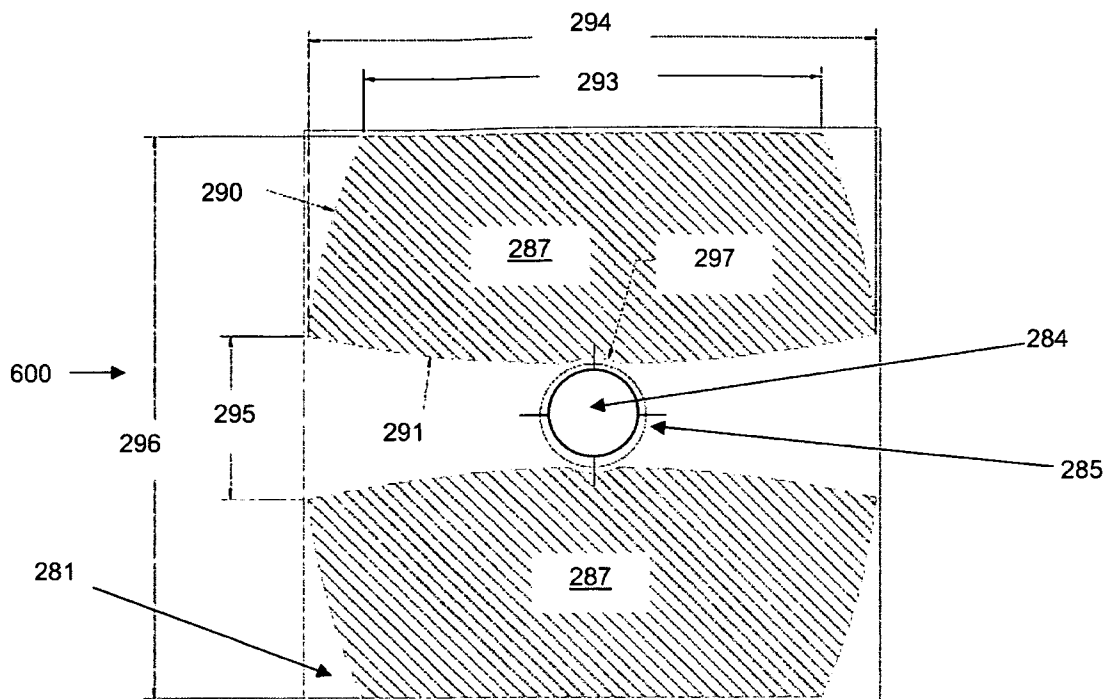


FIG. 35

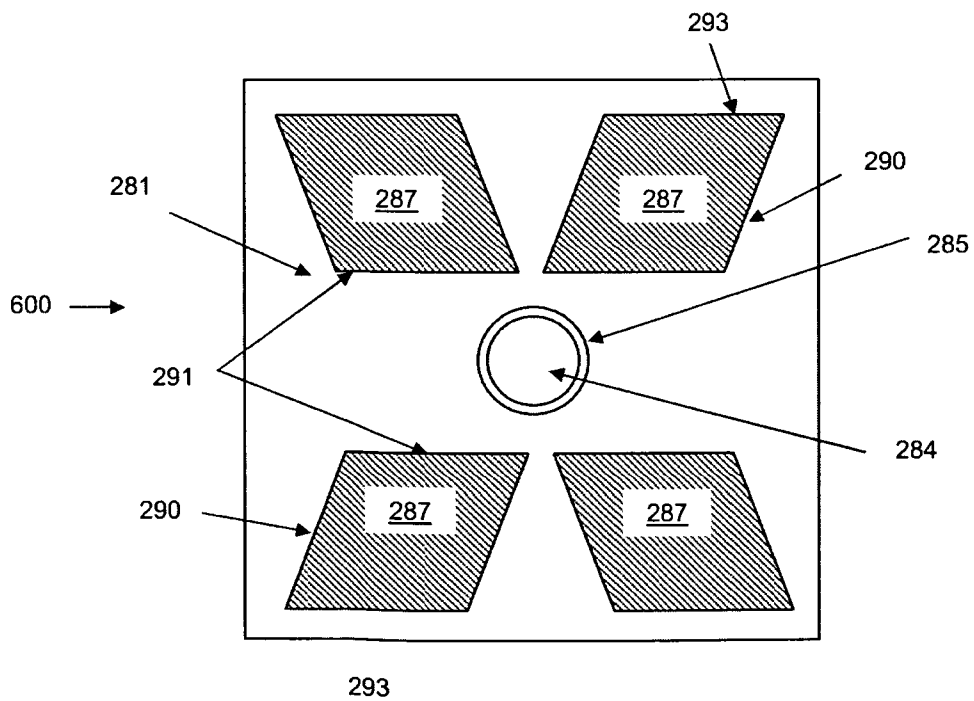
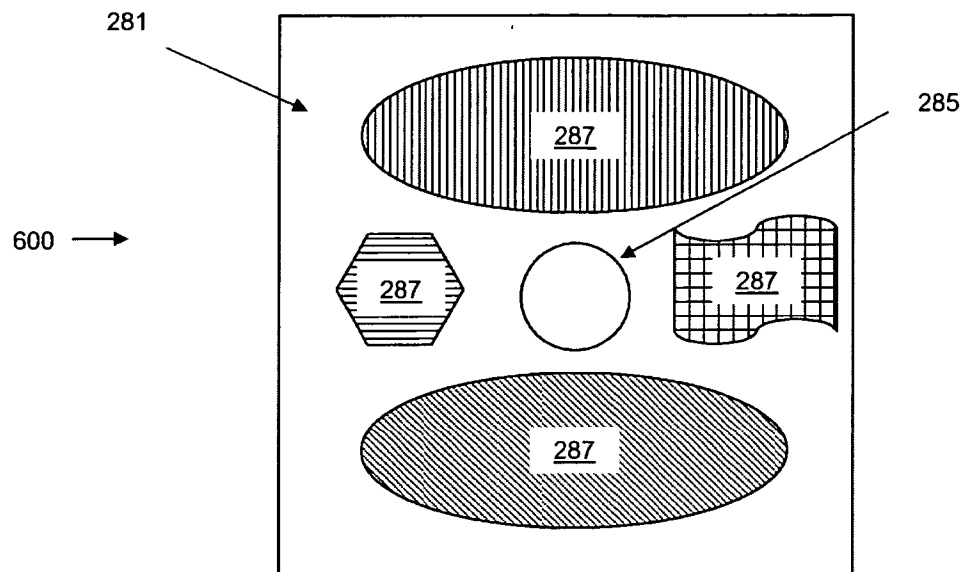
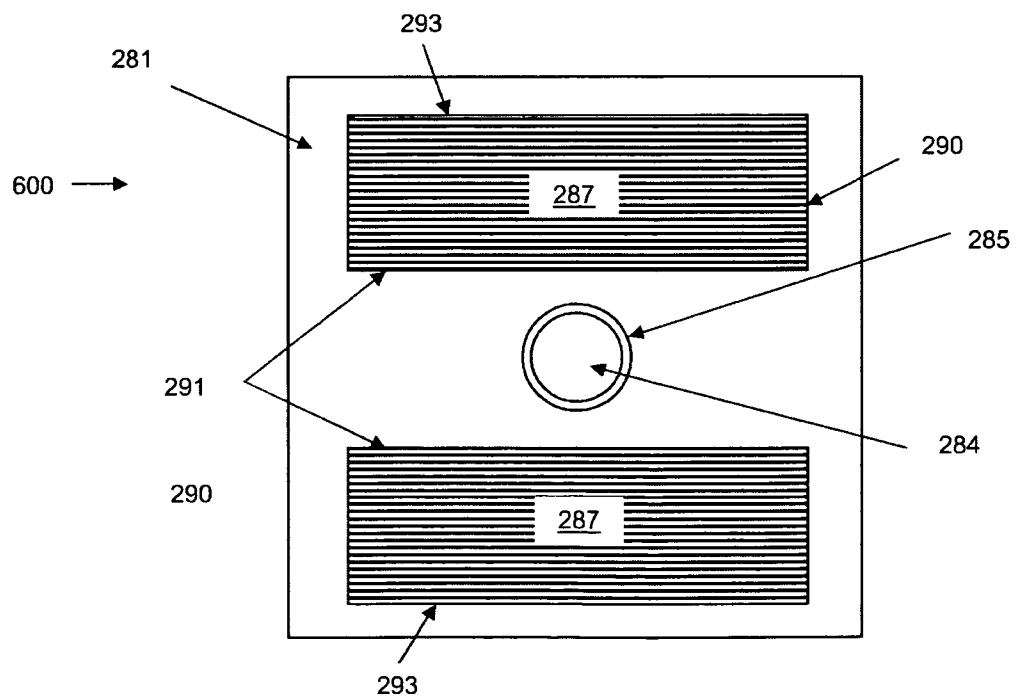


FIG. 36

**FIG. 37****FIG. 38**

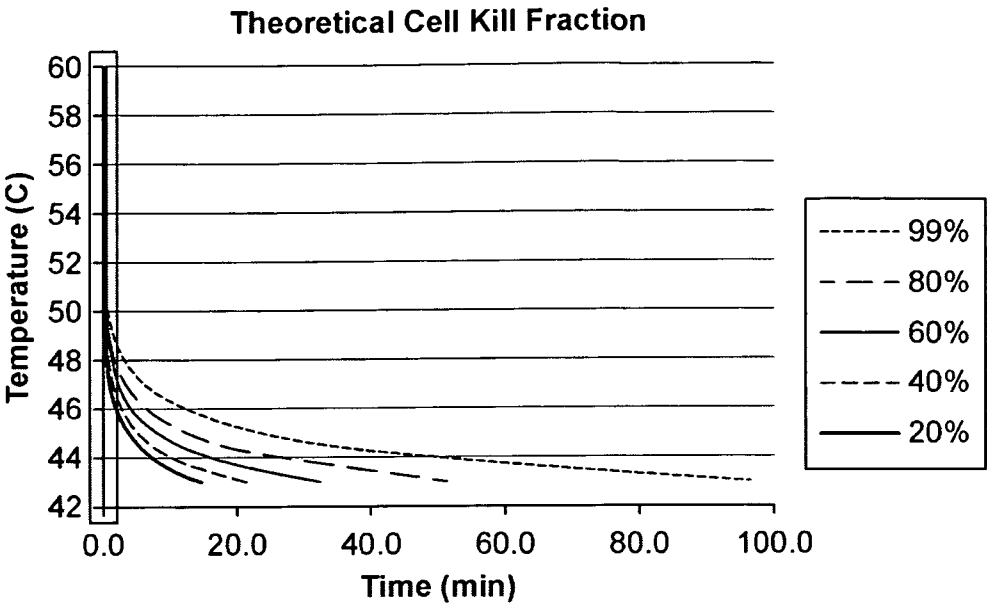


FIG. 39

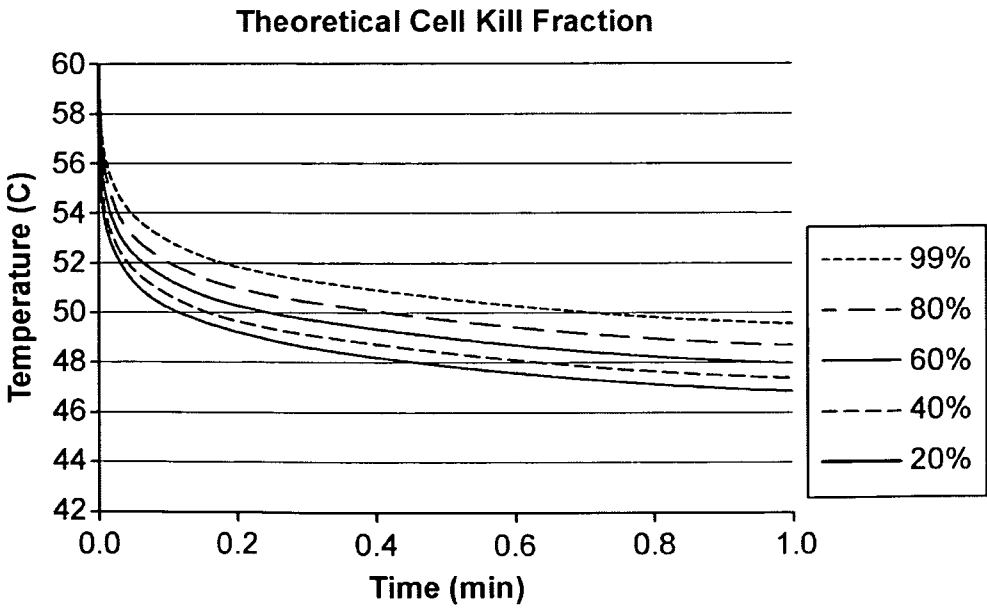


FIG. 40

Isoeffective Dosages To Theoretically Achieve 1% Survival Fraction

Temperature (°C)	Exposure time (min)	Exposure Time (sec)
43	100.00	6000
44	50.00	3000
45	25.00	1500
46	12.50	750
47	6.25	375
48	3.13	188
49	1.56	94
50	0.78	47
51	0.39	23
52	0.20	12
53	0.10	6
54	0.05	3
55	0.02	1

FIG. 41

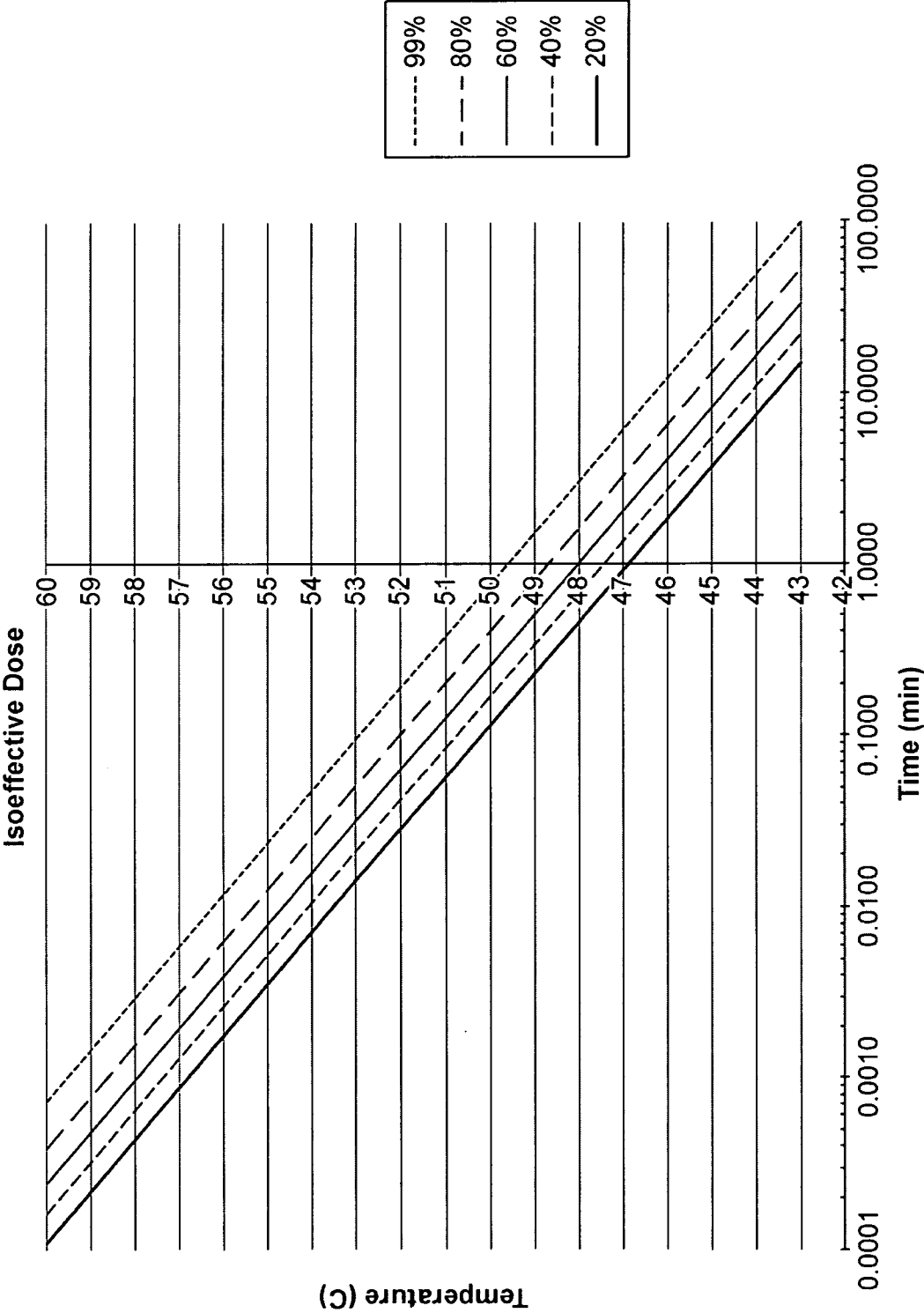


FIG. 42

KZK Simulation of Cylindrical Transducer Output showing Linear Superposition of Multiple Pulse

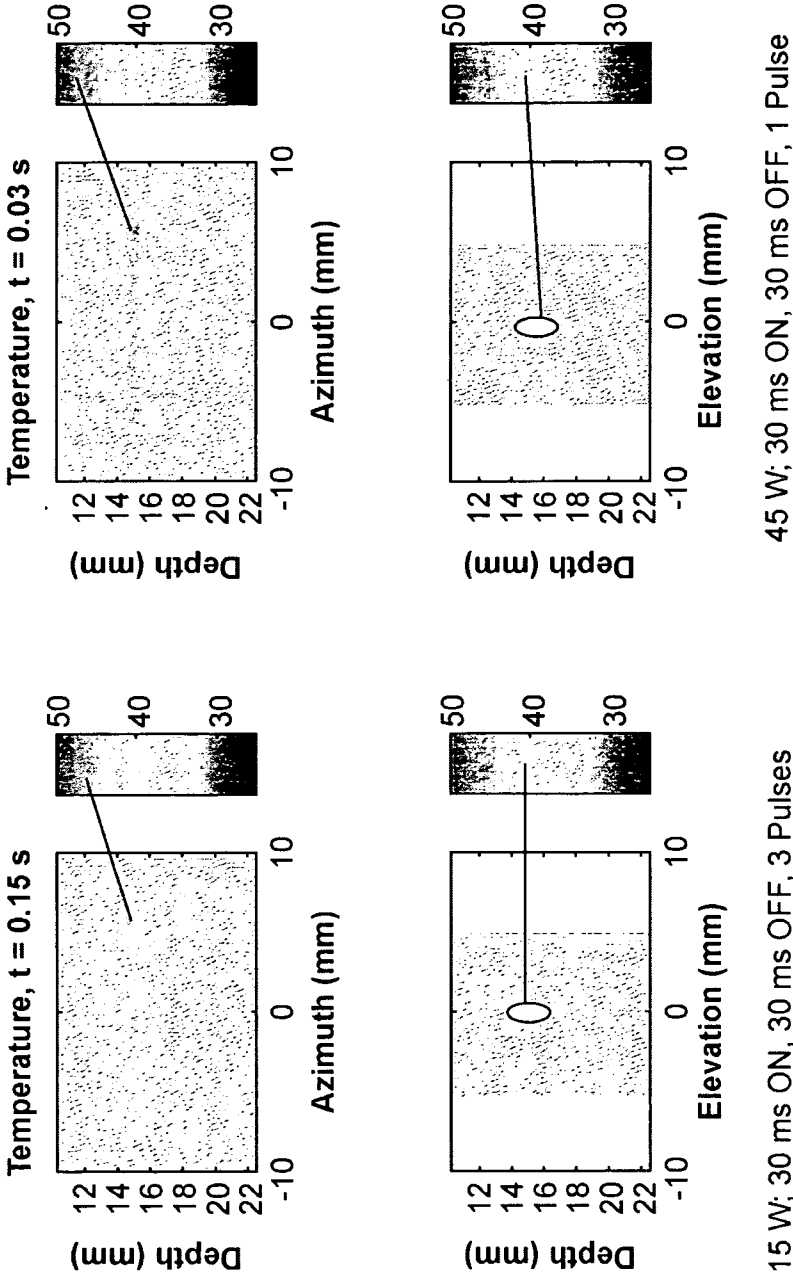


FIG. 43

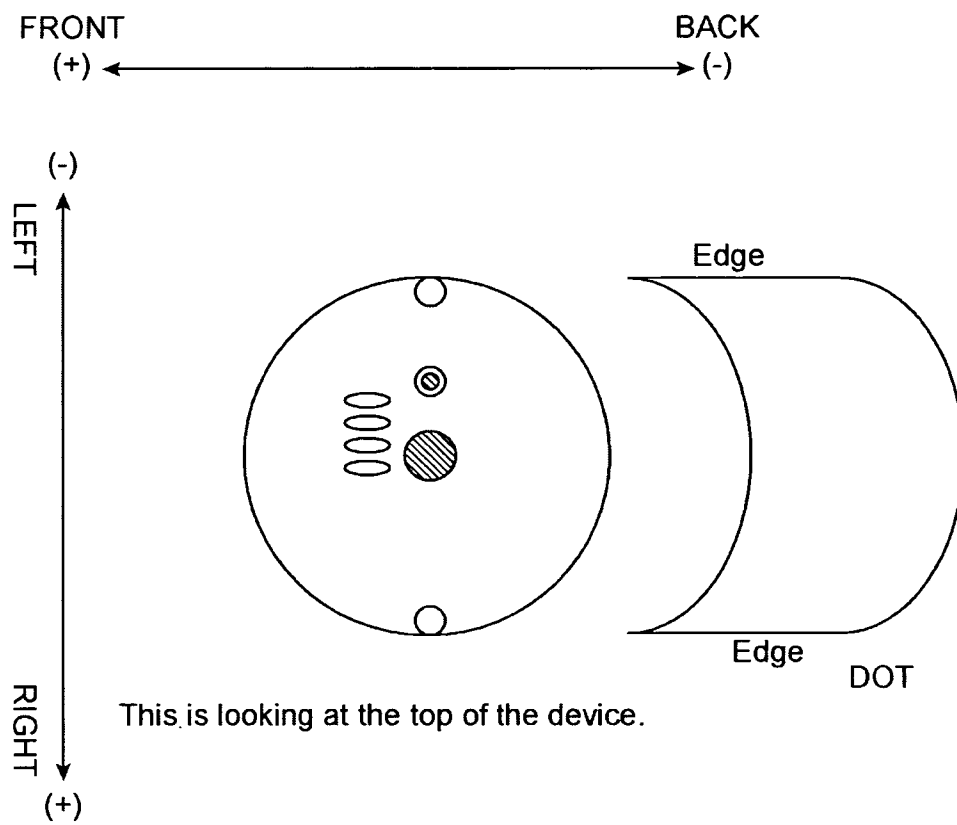
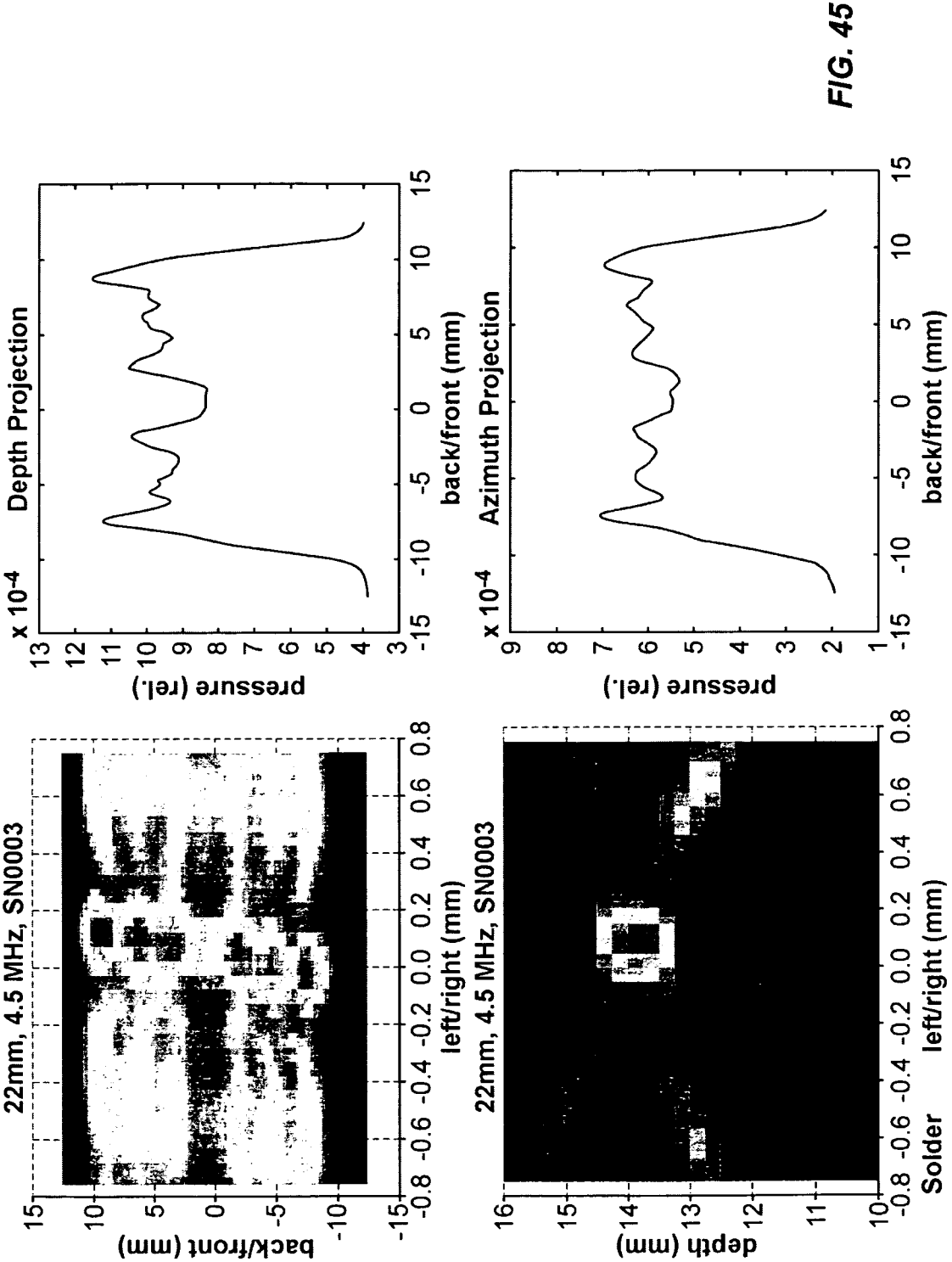


FIG. 44



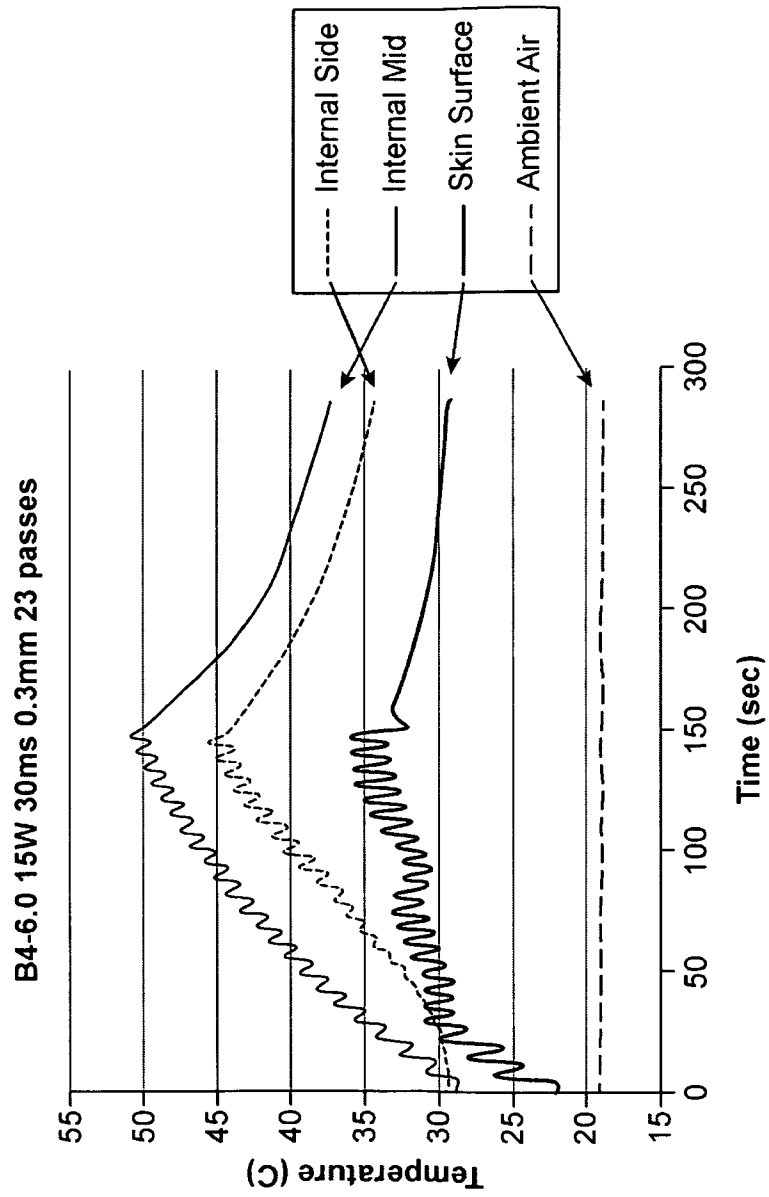


FIG. 46

3-Factor 3-Level DOE to Determine Settings for an Isoeffective Dosage Study

Power	Time-on	Time-off	Spacing	#"TCPs"	Energy/Line	Energy/Pass
[W]	[ms]	[ms]	[mm]	[#]	[J]	[J]
10	30	34	0.3	84	0.3	25.2
15	20	34	0.3	84	0.3	25.2
15	30	34	0.2	125	0.45	56.3
15	30	34	0.3	84	0.45	37.8
15	40	34	0.3	84	0.6	50.4
20	30	34	0.3	84	0.6	50.4
15	30	34	0.1	250	0.45	112.5

FIG. 47

Site	Transducer	SN	Power	Time-on	Spacing	Passes	Pretreatment	Post-treatment	Day 7
30.1	C4.5-22-6.0	SN0002	15	40	0.3	31			

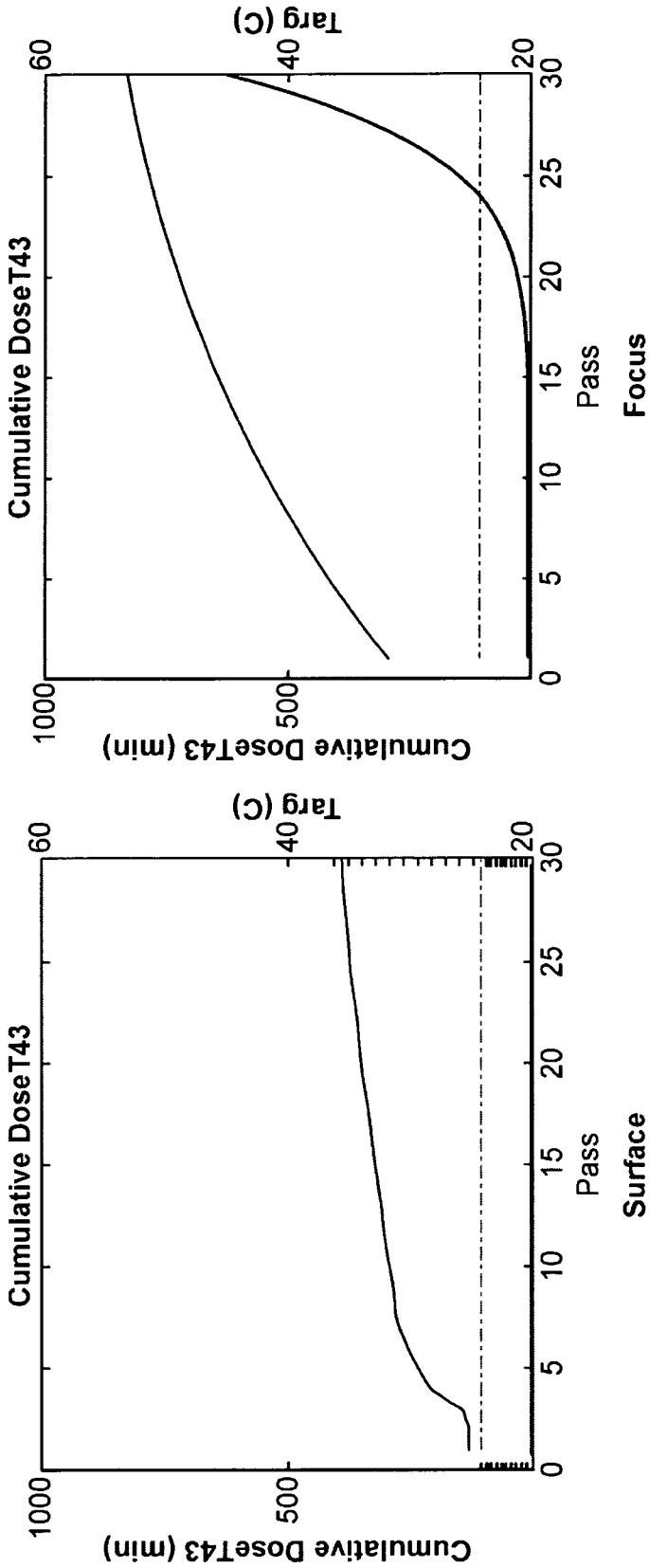


FIG. 48

Time-Temperature Goals for Thermal Dosage Testing

Site	Target Time [min]	Target Time [sec]	Target Temperature [°C]
C1	0.10	6	60
1	5.00	300	45
2	1.00	60	45
3	5.00	300	48
4	1.00	60	48
5	0.20	12	48
6	1.00	60	51
7	0.20	12	52

FIG. 49

3.5Mhz, 22mm width, 6.0mm Depth Cylindrical Transducer
Treatment Settings For Isoeffective Thermal Dosage Study

Power [W]	Time-on [ms]	Time-off [ms]	Spacing [mm]	#"TCPs"	Energy/Line [J]	Energy/Pass [J]
15	30	34	0.3	84	0.45	37.8
15	60	67	0.7	36	0.9	32.4

FIG. 50

Dimensions of Spread of Heat Based on Thermally Overdosed Site

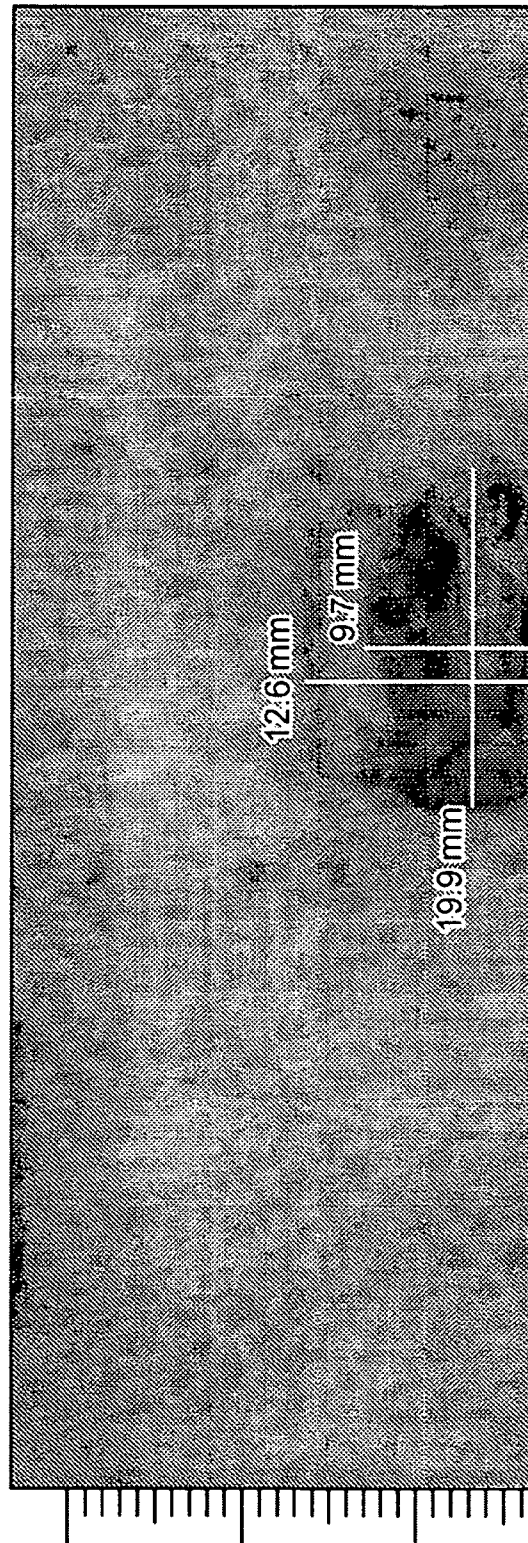


FIG. 51

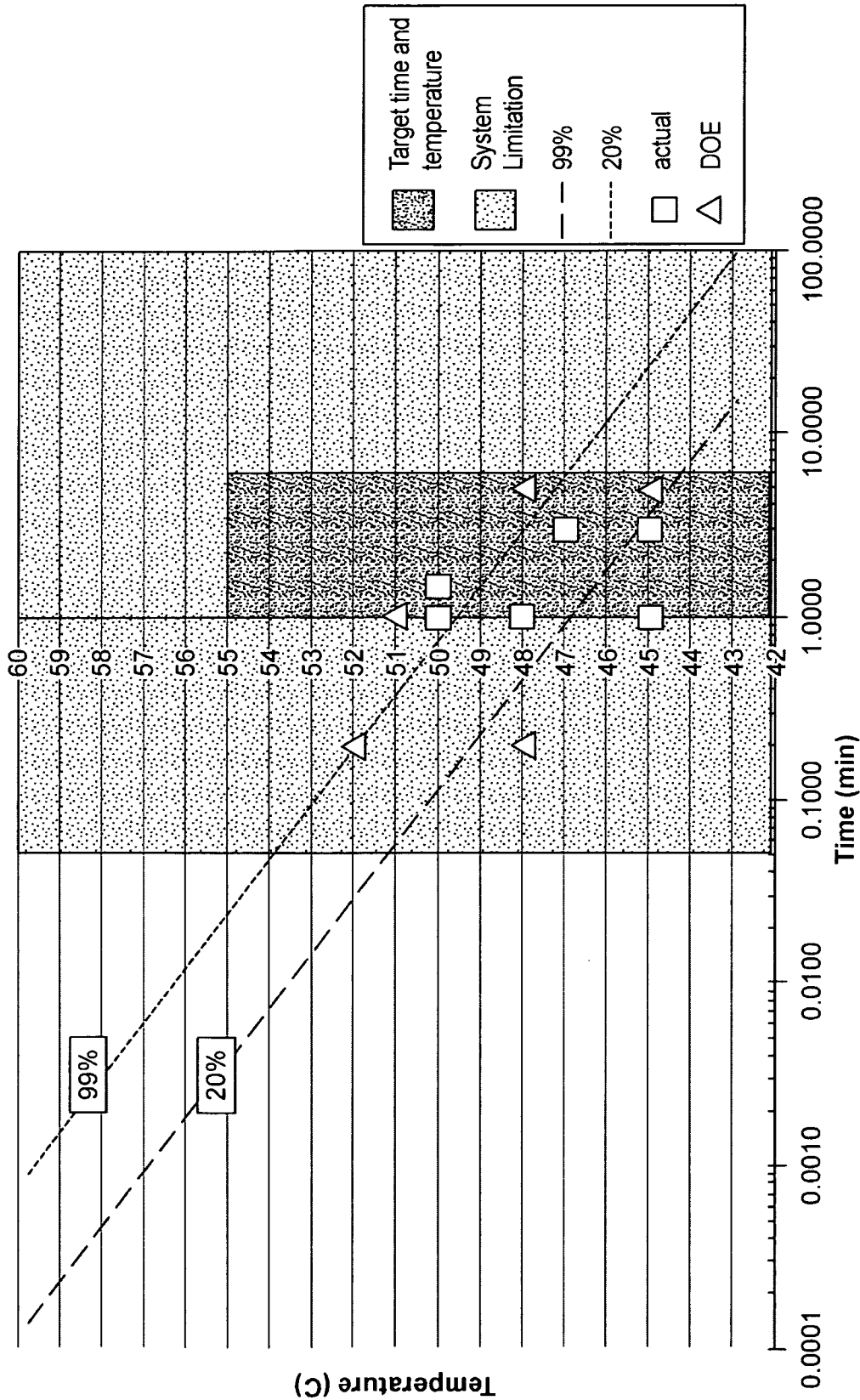


FIG. 52

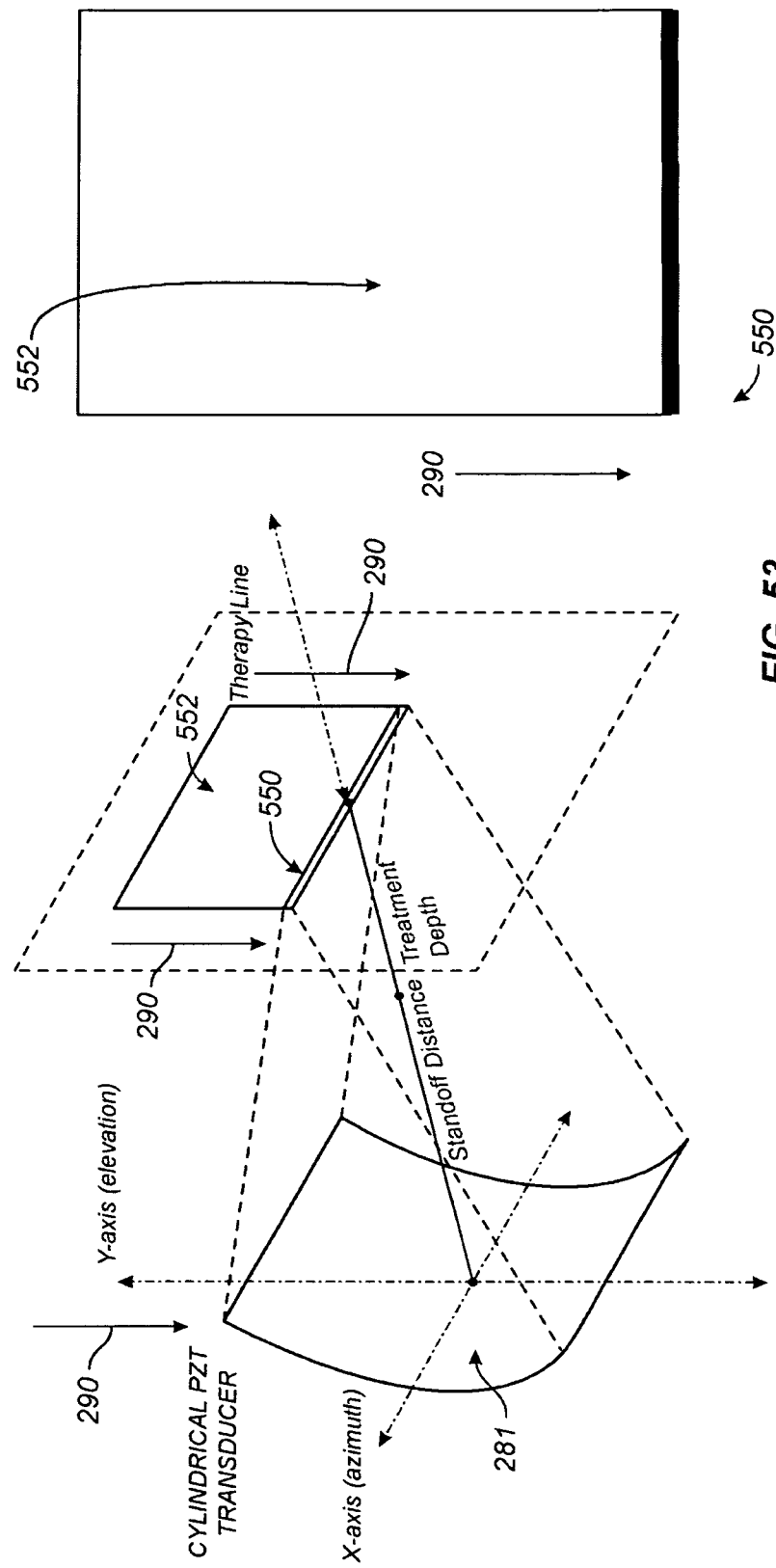


FIG. 53

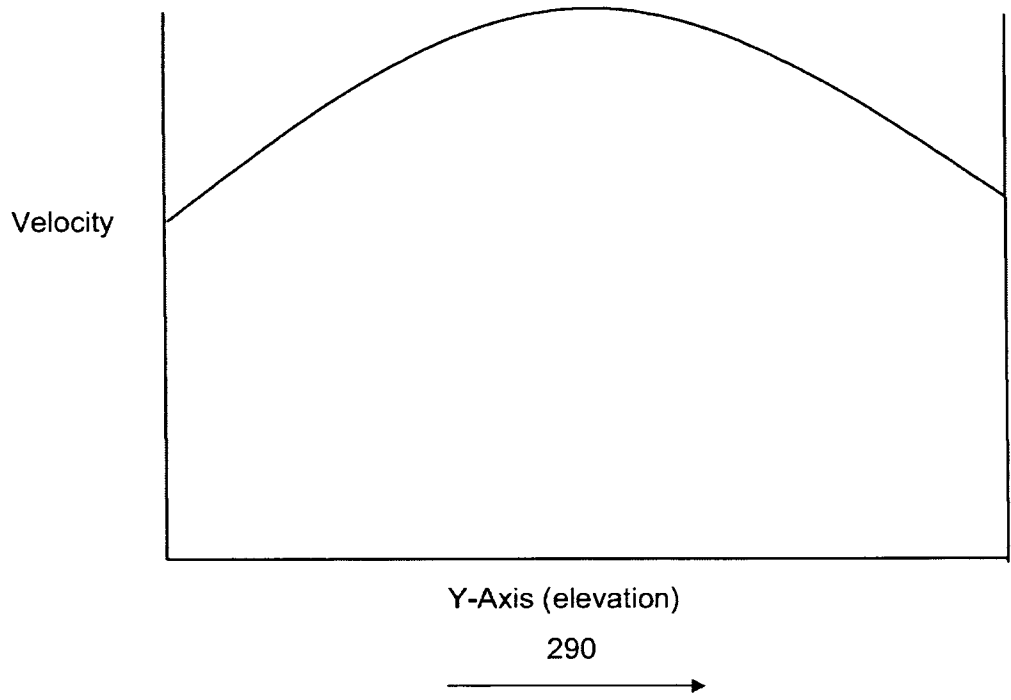


FIG. 54

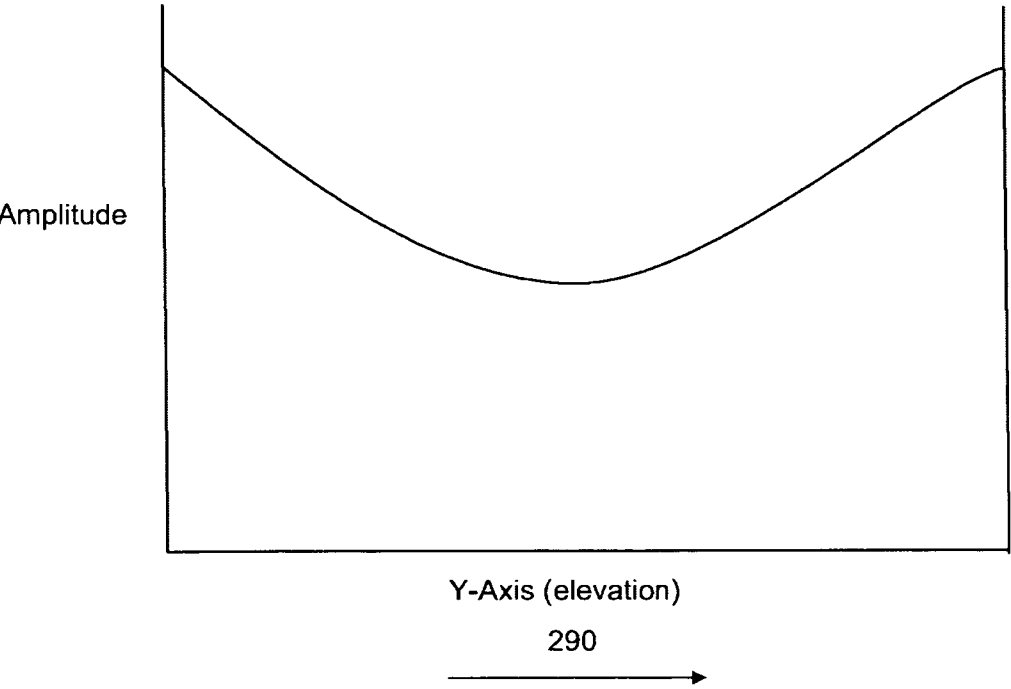


FIG. 55

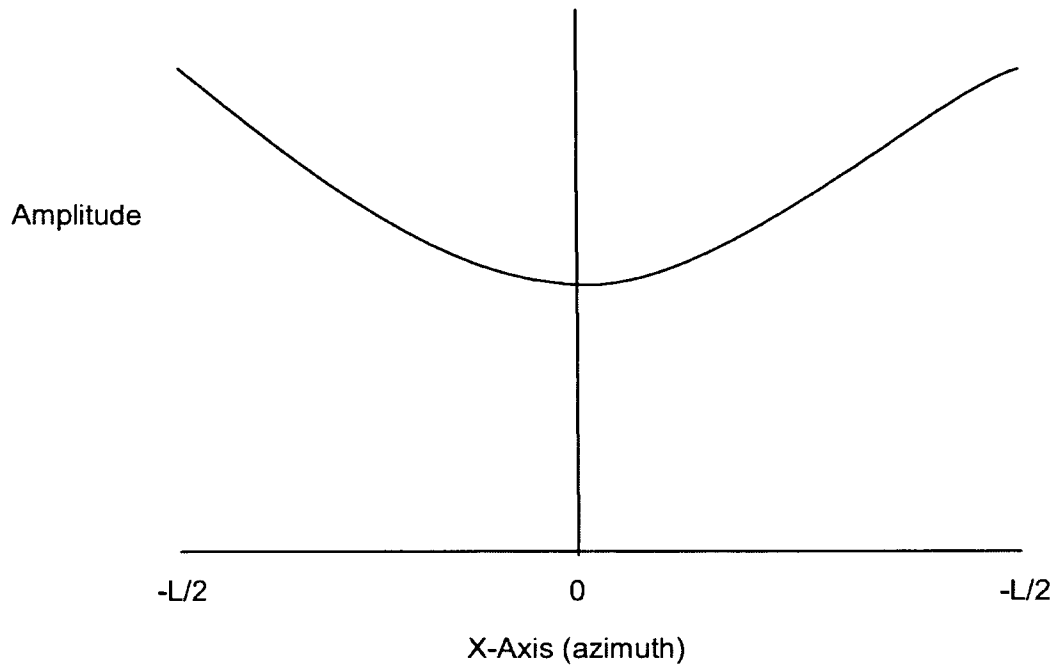


FIG. 56

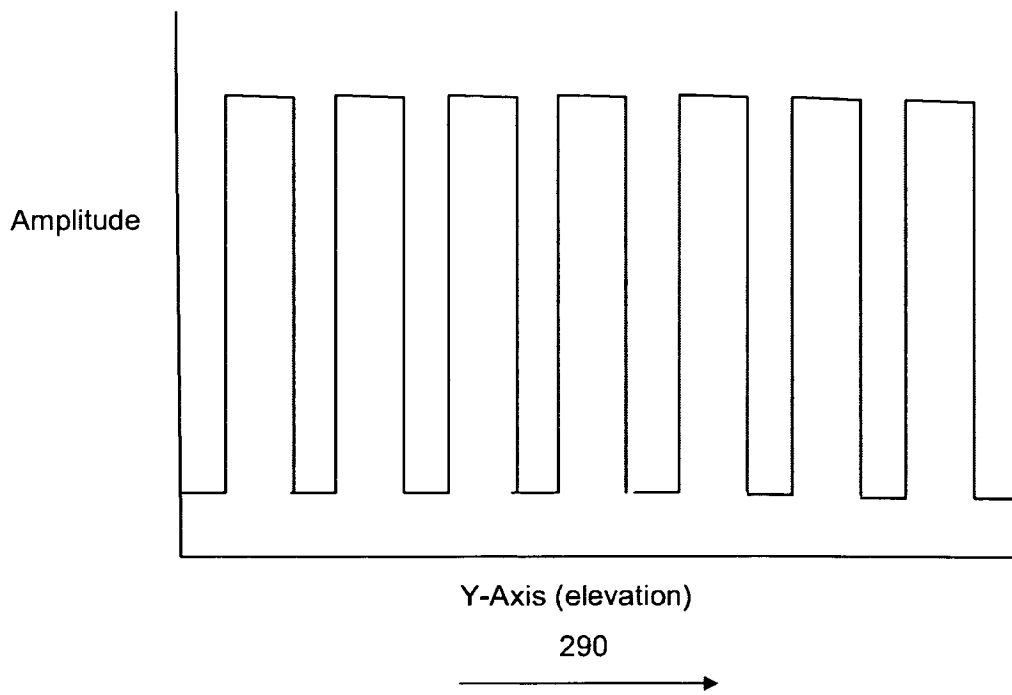


FIG. 57

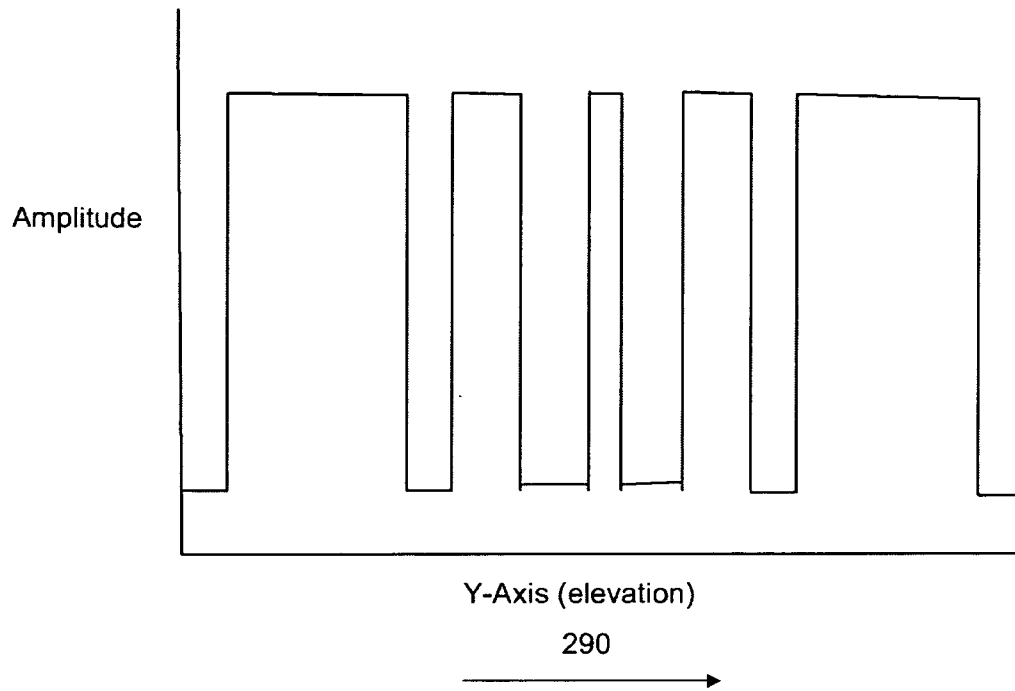


FIG. 58

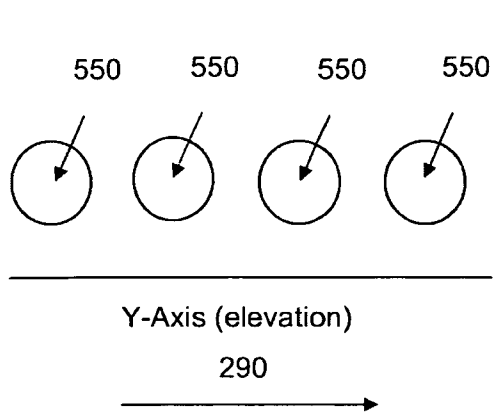


FIG. 59

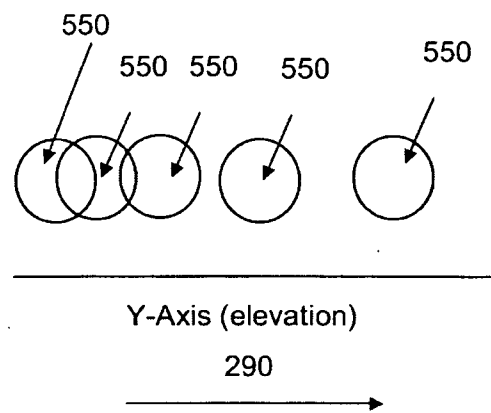


FIG. 60

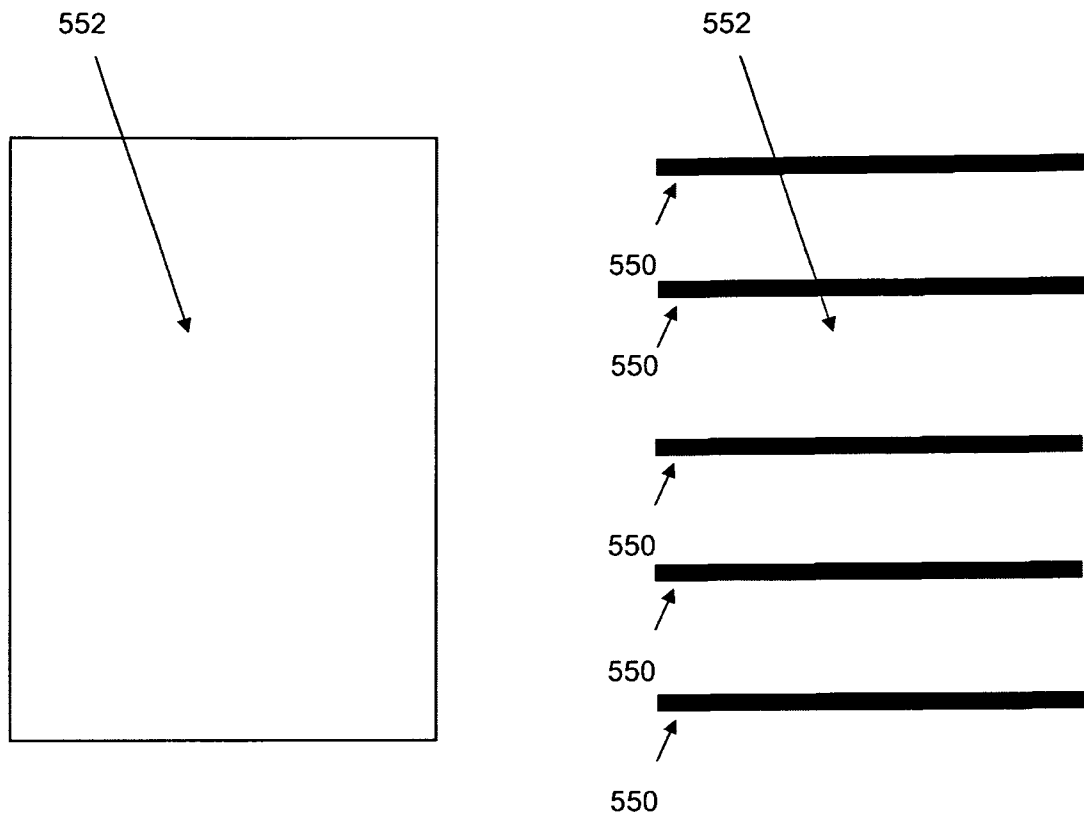


FIG. 61

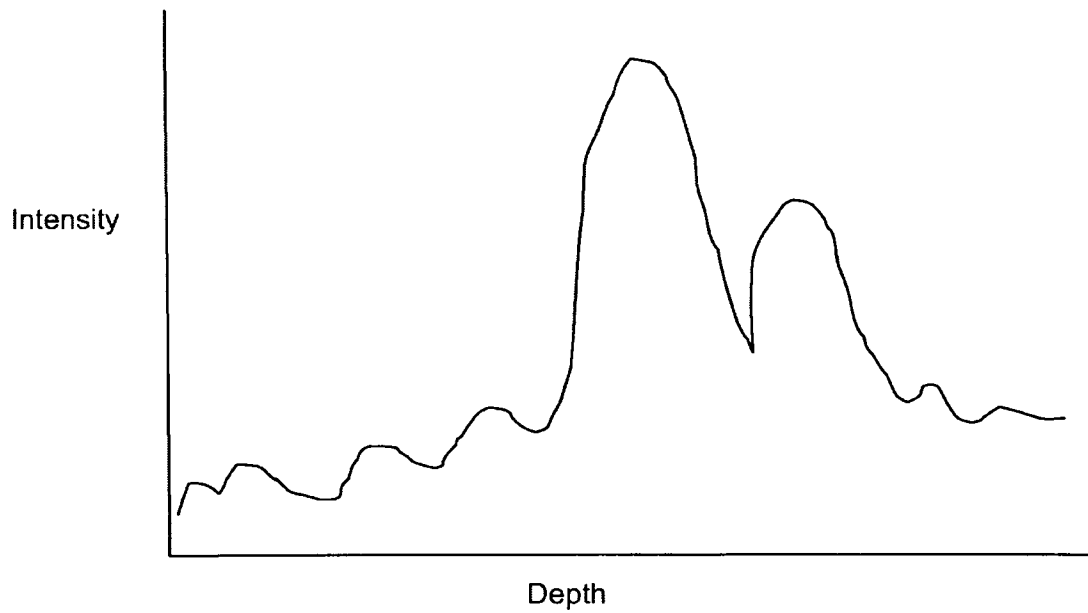


FIG. 62

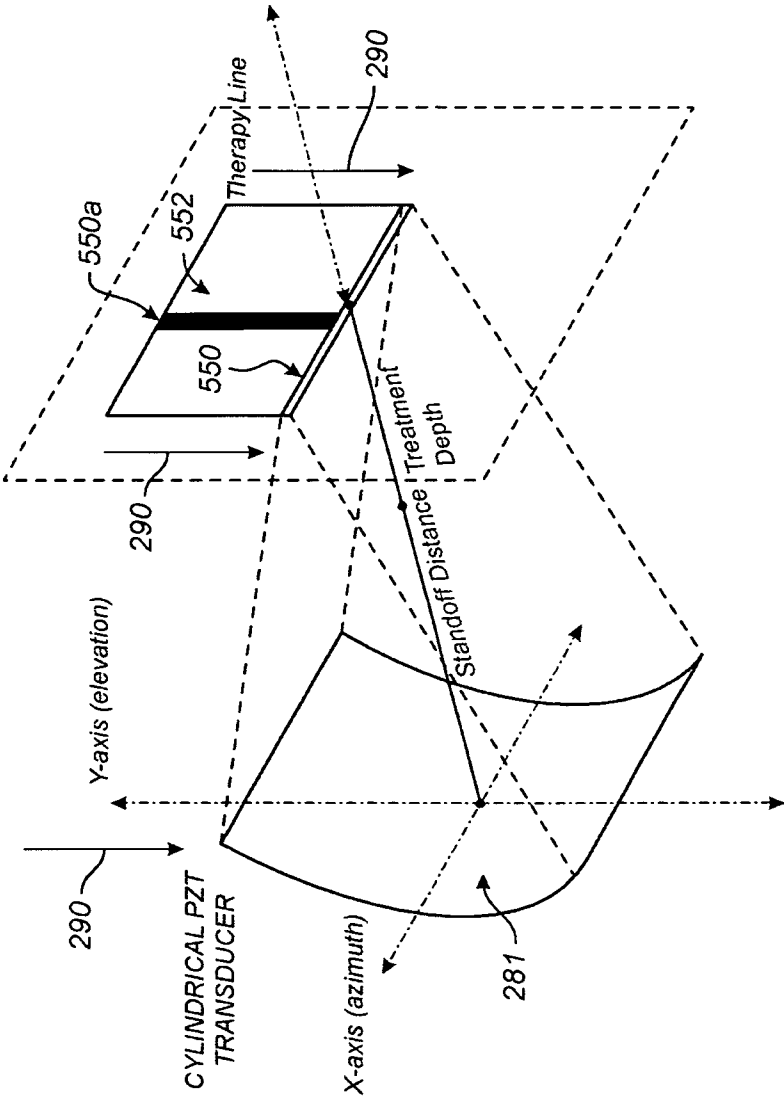


FIG. 63

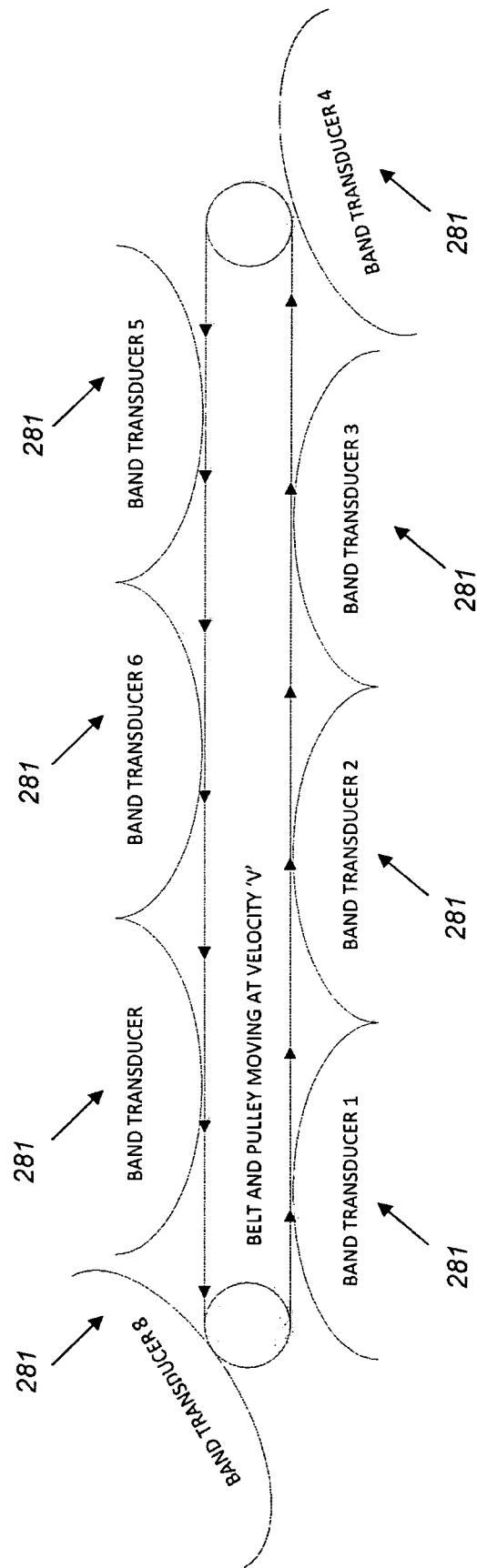


FIG. 64

Figure 65:

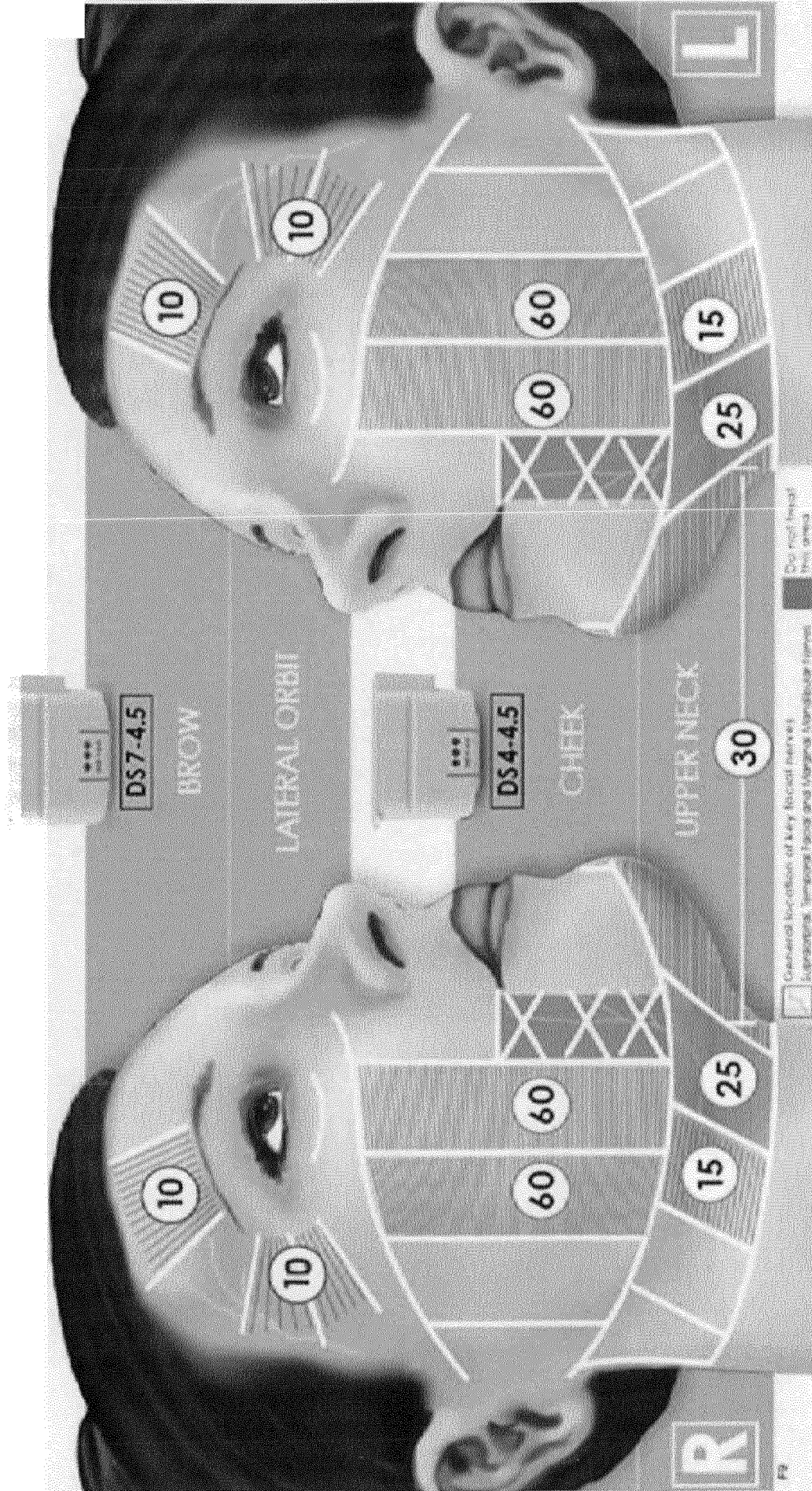


Figure 66:

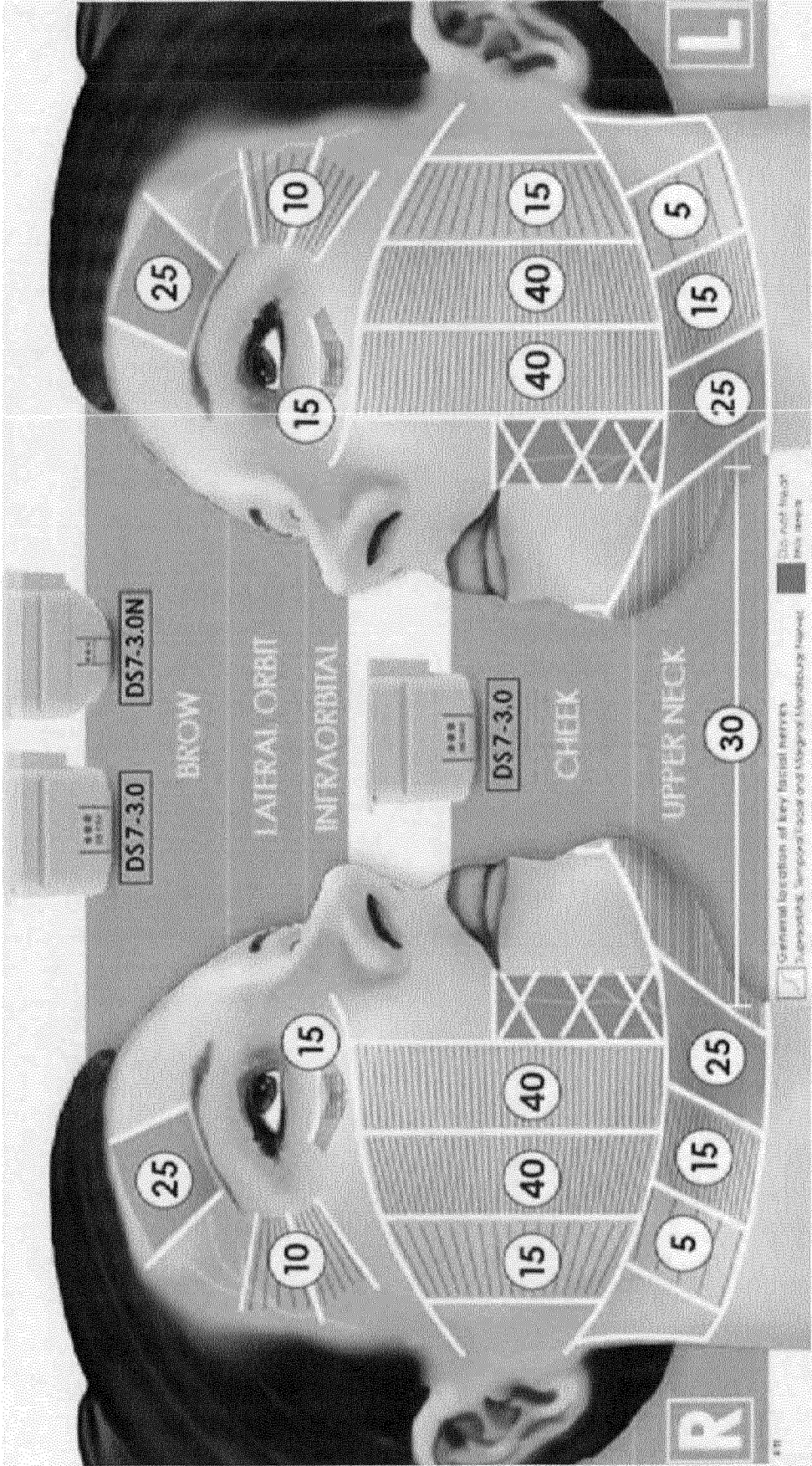


Figure 67:

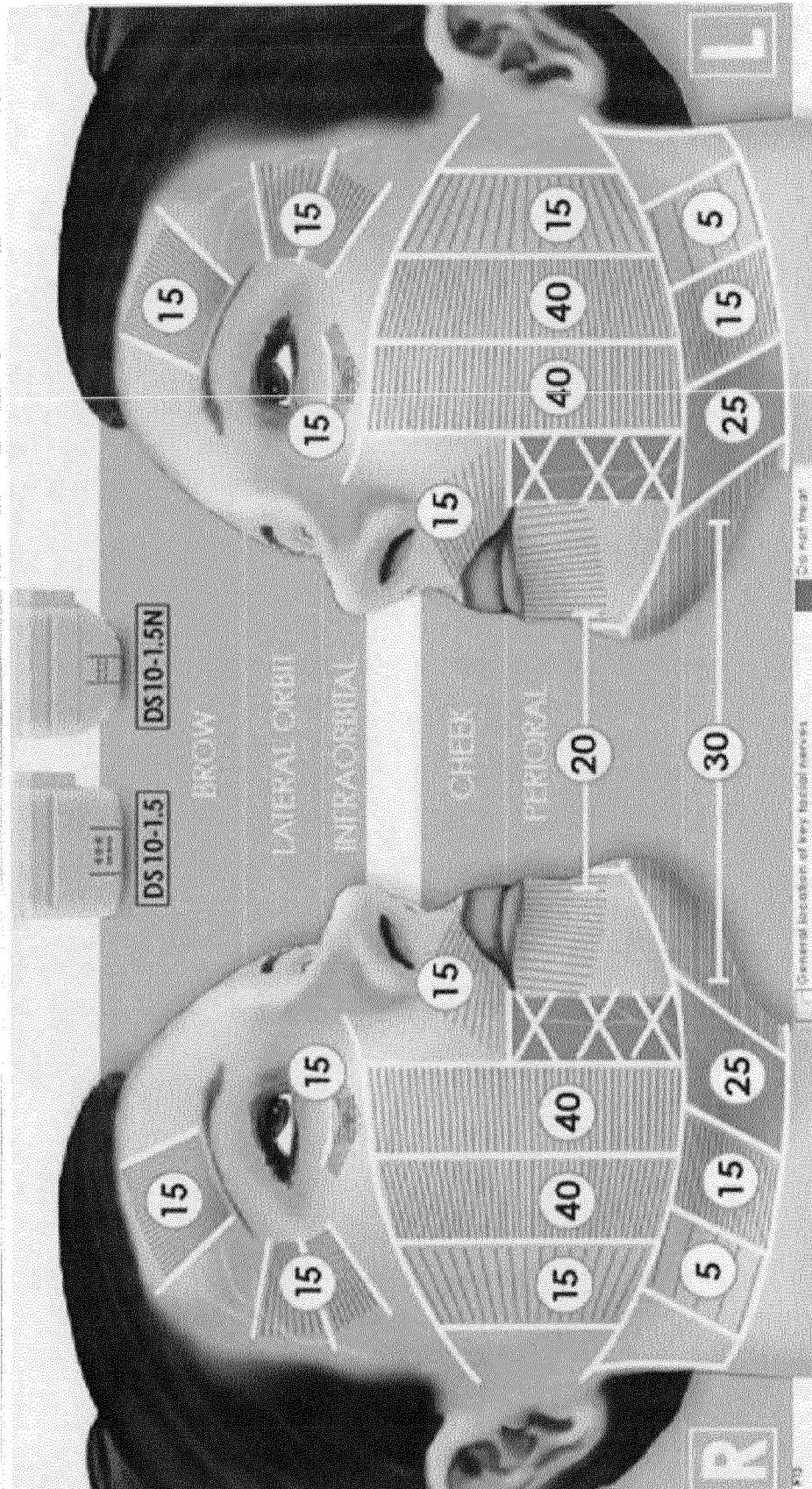


Figure 68:

Treat with the deepest transducer first (DS 4-4.5), then move superficially towards the skin's surface (DS 10-1.5)

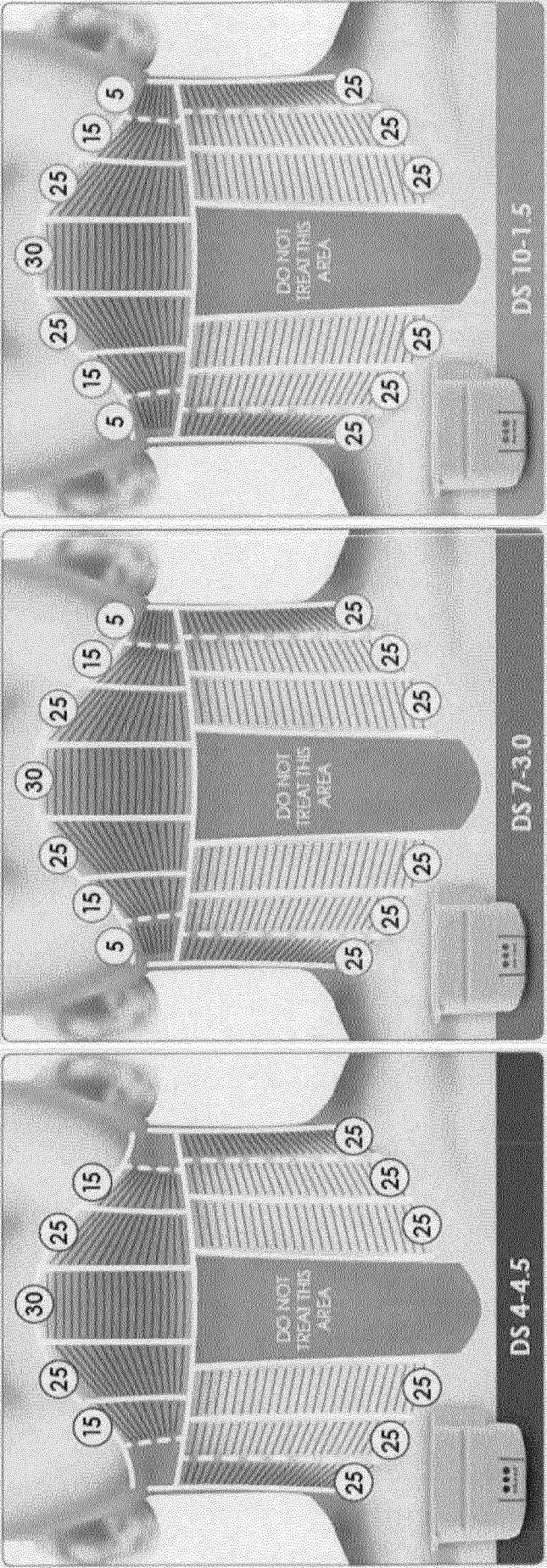
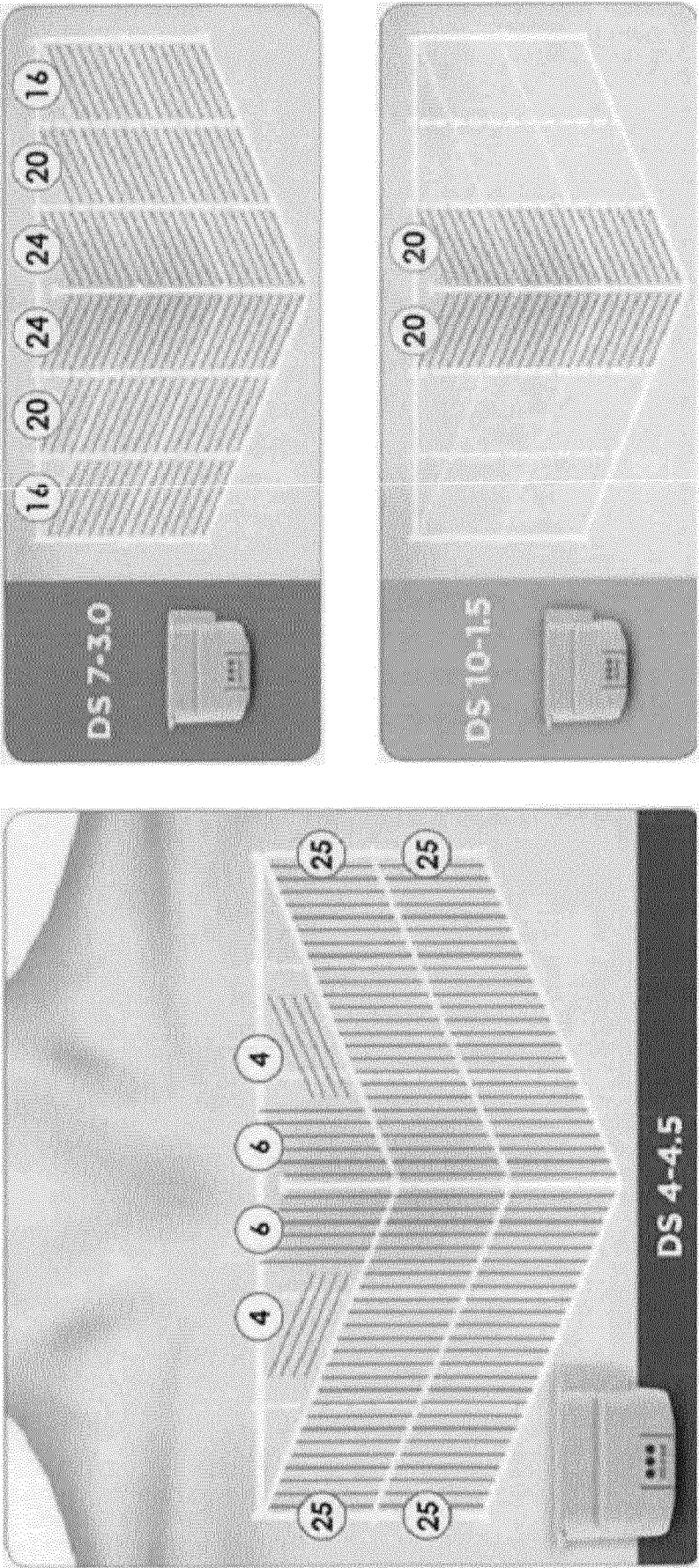


Figure 69:

Treat with the deepest transducer first (DS 4-4.5), then move superficially towards the skin's surface (DS 7-3.0, then DS 10-1.5)



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/001703

A. CLASSIFICATION OF SUBJECT MATTER		
INV. A61N7/02	A61K38/48	A61Q19/08 A61K9/00 C07K14/33
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61N A61K A61Q C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/025919 A1 (DEEM MARK E [US] ET AL) 1 February 2007 (2007-02-01)	1,3-6
Y	paragraphs [0016] - [0028]; figures 1-5 paragraph [0092]; figure 14	7-15
A	----- WO 2004/006954 A2 (ALLERGAN INC [US]; DONOVAN STEPHEN [US]) 22 January 2004 (2004-01-22) page 15, paragraph 1 - page 17, paragraph 1 page 20, paragraph 4 - page 21, paragraph 2 page 29, paragraph 2 - page 32, paragraph 1 example 4 ----- -/-	1,3-15
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 6 January 2017		Date of mailing of the international search report 20/01/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Schnurbusch, Daniel

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/001703

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/096471 A1 (SLAYTON MICHAEL H [US] ET AL) 18 April 2013 (2013-04-18)	7-12
A	paragraphs [0024] - [0039] paragraphs [0055] - [0056] paragraph [0085] paragraphs [0116] - [0117]; figures 6A-B paragraphs [0125] - [0128]; figures 10A-D -----	1,3-6, 13-15
Y	US 2012/016239 A1 (BARTHE PETER G [US] ET AL) 19 January 2012 (2012-01-19) paragraphs [0063] - [0068]; figure 1 paragraphs [0089] - [0100] paragraph [0113]; figure 6 paragraphs [0232] - [0245]; figures 29-30B -----	13-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/001703

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2(completely); 3-15(partially)
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 2(completely); 3-15(partially)

Claims 2 and claims 3-15 when depending on claim 2 relate to a method of treatment by surgery on the human or animal body, because the method of claim 2 includes the surgical step of "[...] applying a clostridial neurotoxin [...]" and (ii) applying ultrasound to the tissue treated [...] to a linear focal zone [...]" . Since this subject-matter is excluded from patentability according to Article 17 (2) PCT and Rule 39.1.(iv) PCT, these claims should be deleted. Furthermore, any reference in the description to this method of treatment by surgery as forming part of the invention should also be deleted or marked explicitly as being exemplary.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/001703

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007025919	A1	01-02-2007	EP 1906923 A2 09-04-2008
			JP 5826450 B2 02-12-2015
			JP 2009502806 A 29-01-2009
			JP 2015186597 A 29-10-2015
			US 2007025919 A1 01-02-2007
			US 2010003282 A1 07-01-2010
			US 2012029261 A1 02-02-2012
			US 2013303948 A1 14-11-2013
			US 2015150625 A1 04-06-2015
			WO 2007014003 A2 01-02-2007
WO 2004006954	A2	22-01-2004	AT 430579 T 15-05-2009
			AU 2003267987 A1 02-02-2004
			BR 0312506 A 12-04-2005
			CA 2492029 A1 22-01-2004
			CN 1668327 A 14-09-2005
			DK 1521593 T3 03-08-2009
			EP 1521593 A2 13-04-2005
			ES 2323497 T3 17-07-2009
			JP 2005538082 A 15-12-2005
			JP 2011037866 A 24-02-2011
			KR 20050025320 A 14-03-2005
			MX PA05000134 A 11-04-2005
			NZ 537231 A 30-04-2008
			US 2004009180 A1 15-01-2004
			US 2005074461 A1 07-04-2005
			US 2005175636 A1 11-08-2005
			US 2006188525 A1 24-08-2006
			US 2008220020 A1 11-09-2008
			WO 2004006954 A2 22-01-2004
US 2013096471	A1	18-04-2013	NONE
US 2012016239	A1	19-01-2012	US 2012016239 A1 19-01-2012
			US 2012035475 A1 09-02-2012
			US 2012035476 A1 09-02-2012
			US 2012046547 A1 23-02-2012
			US 2012053458 A1 01-03-2012
			US 2013303904 A1 14-11-2013
			US 2013303905 A1 14-11-2013
			US 2015374333 A1 31-12-2015